PB82-147778

Epidemiology Feasibility Study
Effects of Noise on the Cardiovascular System
Appendix C, Review of Non-Noise Related Research of Cardiovascular Disease

South Carolina Univ., Columbia

Prepared for

Environmental Protection Agency
Washington, DC

Jul 81

U.S. Department of Commerce
National Technical Information Service
NTIS

BIBLIOGRAPHIC INFORMATION

PB82-147778

Epidemiology Feasibility Study: Effects of Noise on the Cardiovascular System. Appendix C, Review of Non-Noise Related Research of Cardiovascular Disease,

Jul 81

Julian E. Keil, and David M. Propert.

PERFORMER: South Carolina Univ., Columbia.
Contract EPA-68-01-6274

SPONSOR: Environmental Protection Agency, Washington, DC.
Office of Noise Abatement and Control.
EPA-550/981-103C

See also Appendix B, PB82-147760.

This review will present introductory information about the pathology, pathogenesis, and epidemiology of cardiovascular diseases. The primary focus will be a discussion of the key cardiovascular diseases, their manifestations, risk factors, etiology of the risk factors and origin of the precipitants of the diseases. Specifically, the purpose of this 'state-of-the-art' review is to provide an empirical foundation for subsequent noise-related research by: (1) summarizing the current knowledge of the pathogenesis and pathophysiology of the cardiovascular diseases; (2) denoting key confounding and interactive factors which must be considered in the design of future studies; and (3) identifying pathways in the pathogenic process and specifying potential entry points for investigation of noise as one environmental influence on the cardiovascular system.

KEYWORDS: *Cardiovascular diseases, *Stress(Physiology).

Available from the National Technical Information Service, Springfield, Va. 22161

PRICE CODE: PC A06/MF A01

PB82-147778

EPIDEMIOLOGY FEASIBILITY STUDY: EFFECTS OF NOISE ON THE CARDIOVASCULAR SYSTEM

APPENDIX C

REVIEW OF NON-NOISE RELATED RESEARCH OF CARDIOVASCULAR DISEASE

EPA 550/9-81-103 C

By: Julian E. Keil, Dr. PH.
David M. Propert, M.D.

Principal Investigator: Shirley J. Thompson, Ph.D.

July 1981

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA 22161

EPIDEMIOLOGY FEASIBILITY STUDY:
EFFECTS OF NOISE ON THE CARDIOVASCULAR SYSTEM

APPENDIX C

REVIEW OF NON-NOISE RELATED RESEARCH OF CARDIOVASCULAR DISEASE

By: Julian E. Keil, Dr. PH.
David M. Propert, M.D.

Principal Investigator: Shirley J. Thompson, Ph.D.

July 1981

TABLE OF CONTENTS

		Page
1.	INTRODUCTION	C-1
2.	CARDIOVASCULAR DISEASES: PATHOPHYSIOLOGY AND PATHOGENESIS	C-2
	2.1 Atherosclerosis	C-3
	2.2 Ischemic Heart Disease	C-8
	2.2.1 Basic Dynamics	C-8
	2.2.2 Acute Myocardial Infarction	C-11
	2.2.3 Angina Pectoris	C-12
	2.2.4 Sudden Death	C-12
	2.3 Stroke	C-13
	2.4 Hypertension	C-16
	2.4.1 Classification and Sequellae	C-16
	2.4.2 Etiology of Primary Hypertension	C-18
	2.4.3 Blood Pressure Control and Pathogenesis	C-20
3.	CARDIOVASCULAR DISEASES: EPIDEMIOLOGY	C-26
	3.1 Ischemic Heart Disease	C-26
	3.1.1 Acute Myocardial Infarction	C-29
	3.1.2 Angina Pectoris	C-32
	3.1.3 Sudden Cardiac Death	C-34
	3.1.4 Atherogenesis	C-36
	3.1.5 Cholesterol and Lipids	C-37
	3.2 Stroke	C-45
	3.3 Hypertension	C-49
	3.3.1 Epidemiologic Definitions	C-49
	3.3.2 Clinical Definitions	C-50
	3.3.3 Measurement of Blood Pressure	C-51
	3.3.4 Distributions and Patterns by Age, Race, Sex Residence	C-53
	3.3.5 Risks Associated with Hypertension	C-58
	3.3.6 Possible Etiology	C-61
	3.4 Risk Factors	C-67
	3.4.1 Smoking	C-67
	3.4.2 Alcohol	C-67
	3.4.3 Oral Contraceptives	C-68
	3.4.4 Obesity	C-69
	3.4.5 Physical Activity	C-69
	3.4.6 Environment	C-70
	3.4.7 Stress	C-71
	3.4.8 Social Class	C-71
	3.4.9 Life Events	C-74
	3.4.10 Personality Type	C-75
	3.5 Summary	C-77
	SELECTED REFERENCES	C-79

LIST OF ILLUSTRATIONS

Figure		Page
C-1	Pathogenesis of Atherosclerotic Plaque	C-7
C-2	Major Determinants of Oxygen Demand and Supply to the Myocardium	C-9
C-3	Results of Myocardial Ischemia	C-10
C-4	Factors Influencing Cardiac Output and Peripheral Resistance	C-21
C-5	Mechanisms in the Development of Essential Hypertension	C-25
C-6	Age-Adjusted Death Rates for Ischemic Heart Disease by Race and Sex: United States, 1950-1976	C-27
C-7	Age-Adjusted Death Rates for Cerebrovascular Disease, United States, 1940-1976	C-28
C-8	Relationship Between Average per Capita Availability of Calories from Principal Animal Sources	C-39
C-9	Relation of Dietary Cholesterol to Aortic Intimal Thickening, Measured as Area in Transverse Microscopic Sections	C-40
C-10	Frequency Polygon of Blood Pressure in Charleston County, S.C. Residents, 1960	C-54
C-11	Arterial Blood Pressure by Age of Selected Primitive, Developing and Modern Populations	C-56

LIST OF TABLES

Table		Page
C-1	Some Factors Which Have Been Shown to Injure Endothelium and Increase Permeability to Lipoproteins	C-6
C-2	Distribution of Sudden Deaths	C-14
C-3	Types of Hypertension	C-17
C-4	Clinical Disorders Associated with Hypertension	C-19
C-5	Annual Incidence of AMI in Selected Communities	C-30
C-6	Risk Factors for Ischemic Heart Disease	C-31
C-7	Incidence and Prevalence of Stroke for Males and Females by Age Group, Rochester, Minnesota, 1973	C-47

LIST OF ABBREVIATIONS

AMI	Acute Myocardial Infarction
AP	Angina Pectoris
CHD	Coronary Heart Disease
CNS	Central Nervous System
CV	Cardiovascular Disease
dl	Deciliter
EKG	Electrocardiogram
HDFP	Hypertension Detection and Follow-up Program
HDL	High Density Lipoprotein
Hg	Mercury
IHD	Ischemic Heart Disease
Kcal	Kilogram Calories
LVH	Left Ventricular Hypertrophy
Mg	Milligram
mm	Millimeters
(M $\dot{V}O_2$)	Myocardial Oxygen Consumption
OC	Oral Contraceptives
PGI_2	Prostaglandin Prostocyclin
PRA	Plasma Renin Activity
RR	Relative Risk
SD	Sudden Death
SES	Social Class or Socioeconomic Status
TIA	Transient Ischemic Attack
T_xA_2	Thromboxane A_2
VA	Veteran's Administration
VPC	Ventricular Premature Contractions

1. INTRODUCTION

This review will present introductory information about the pathology, pathogenesis, and epidemiology of cardiovascular diseases. The primary focus will be a discussion of the key cardiovascular diseases, their manifestations, risk factors, etiology of the risk factors and origin of the precipitants of the diseases.

Specifically, the purpose of this "state-of-the-art" review is to provide an empirical foundation for subsequent noise-related research by: (1) summarizing the current knowledge of the pathogenesis and pathophysiology of the cardiovascular diseases; (2) denoting key confounding and interactive factors which must be considered in the design of future studies; and (3) identifying pathways in the pathogenic process and specifying potential entry points for investigation of noise as one environmental influence on the cardiovascular system.

Thus, we will present a review of the literature describing the various physiological and biochemical factors associated with cardiovascular disease pathogenesis together with epidemiologic rationale for and against the risk agents. The authors have examined review articles and other selected papers published in the last three years, but in addition, have included information from classic papers of earlier years from their extensive reprint files.

First, the pathophysiology of each major cardiovascular disease or physiologic state is addressed. This is followed by a succinct discussion of the epidemiology including incidence, prevalence, and secular trends as well as the major risk factors for the emergence of cardiovascular diseases in human populations.

2. CARDIOVASCULAR DISEASES: PATHOPHYSIOLOGY AND PATHOGENESIS

Human response to environmental factors may produce disease through one of three basic mechanisms: (1) contact with potentially toxic, infectious, or immunologically active substances such as bacteria, chemicals, or radiation via the oral, dermal, or inhalation routes; (2) direct mechanical or structural injury by trauma; and (3) stimulation of the central nervous system (CNS) through the various sensing systems. This CNS stimulation may produce physiologic changes at a subconscious level or stimulation of higher integrative cortical functions resulting in emotionally mediated physiologic responses that may precipitate, or induce clinical disease.

An environmental factor such as noise may produce two types of health effects. First, it may produce changes which lead directly to disease processes (etiologic). Secondly, it may precipitate or initiate a particular illness in a person with previously subclinical or clinically stable disease (for example, cardiac arrhythmias, sudden death, heart failure, and episodes of angina pectoris in patients with ischemic heart disease). The health effects of noise may be mediated through the sensori-neural systems via the central nervous system, primarily as noise is sensed by the auditory system. These effects may be mediated by direct stimulation of the CNS by the sound, causing subconscious responses; or indirectly by the effects of the perception of sound on higher cortical functions with interpretation causing the individual to respond to noise as a "stress". Both may initiate a series of neural or humoral changes which affect the cardiovascular system.

Diseases of the cardiovascular system in which no single etiologic factor has been identified, but for which there is indication that the individual's interaction with his environment seems to play a role are (1) ischemic heart disease consisting of acute myocardial infarction, angina pectoris, and sudden cardiac death; (2) stroke; and (3) hypertension and hypertensive vascular disease. In the case of ischemic heart disease and stroke, atherosclerosis is the most common underlying process with hypertension affecting the rate of development of atherosclerosis as well as being a major etiologic factor in certain types of strokes. However, changes in hemodynamics and electrophysiologic abnormalities also are important factors in the genesis of ischemic heart disease with and without serious atherosclerosis.

2.1 Atherosclerosis

Atherosclerosis, a thickening and induration of the arterial wall is the most common form of arteriosclerosis and is the underlying disorder producing ischemic heart disease and many forms of cerebrovascular disease (stroke). The lesion is particularly common in the arch of the aorta at the origin of its branches, the abdominal aorta and its bifurcation with the iliacs, the middle portion of the femoral artery, and the popliteal artery above the knee joint. The epicardial portions of the coronary arteries and the cerebrovascular vessels (primarily the carotid, vertebral and basilar arteries) are particularly susceptible to atherosclerosis.

The process of atherosclerosis occurs in the intimal layer with secondary changes in the media. It progresses from (1) the fatty streak, (2) the fibrous plaque to (3) the complicated lesion. The fatty streak is common to all persons at an early age and represents local collection of smooth muscle cells in the intima. The muscle cells contain lipid and are

surrounded by deposits of lipid in the interstitial areas. This is an asymptomatic lesion found early in life which increases with age but does not appear to cause clinical disease. The lipid is primarily in the form of cholesterol and cholesterol esters.

The fibrous plaque is not as common as the fatty streak among world populations, but is the major pathologic lesion in ischemic heart disease and stroke. It consists of an accumulation of lipid-filled smooth-muscle cells surrounded by lipid, collagen, elastic fibers and ground substance (proteoglycans). The cellular elements form a fibrous cap which covers deep deposit of extracellular lipid and cell debris.

The complicated lesion is a fibrous plaque that has been altered because of hemorrhage, calcification, cell necrosis, ulceration and mural thrombosis. The atherosclerotic fibrous plaque and complicated lesion produce clinical symptoms by (1)occlusion of the vessel lumen, (2)embolization of mural thrombi, or lipid material, calcium and other debris from the plaque and (3)abnormal widening of the vessel (aneurysm) with rupture due to destruction of elastic fibers in the media of the arteries.

The pathogenesis of the atherosclerotic plaque is not completely understood, but there are several hypotheses for which there is experimental support. A basic process appears to be the migration and proliferation of arterial smooth muscle cells from the media into the intima. These muscle cells produce collagen, elastic fiber proteins and ground substance. Unclear is the stimulus for this proliferation and migration, but factors which appear to be involved are low density lipoproteins for which the smooth muscle cells have receptors and which stimulate the cells to produce collagen, elastin and proteoglycans. It appears that certain peptides released by platelets (platelet factor) also stimulate the growth of these cells.

Endothelial injury may be a precipitating factor in this process which results in platelet aggregation with a release of "platelet factor" which, in turn, stimulates growth of the smooth muscle cells. The observation that fibrous plaques occur in areas of potential endothelial trauma due to hemodynamic influences such as at bifurcations supports this theory. Since the endothelium also forms a barrier to passage of blood constituents into the arterial wall, endothelial damage will allow the blood constituents such as lipids to directly pass into the intima and media and stimulate the intimal proliferation of muscle cells. In addition, the plasma constituents apparently accumulate in the smooth muscle cells and the surrounding connective tissue. There is also evidence that hypercholesterolemia in itself may injure the endothelium with the subsequent initiation of platelet adherance and aggregation as outlined above. Factors other than mechanical stress leading to endothelial damage include genetic predisposition in certain patients with hyperlipidemias especially those with predominance of low density lipoproteins. High density lipoproteins appear to play a "protective role". Toxic factors such as nicotine may induce necrosis of endothelial cells. Hypertension may play a role in endothelial damage and thereby accelerate atherosclerosis. Table C-1 shows some of the factors which may injure endothelium and increase permeability to lipoproteins. Figure C-1 illustrates the process and interactions.

In addition to the response to injury hypothesis outlined above, two other hypotheses have been proposed for the atheromatous plaque.

The monoclonol hypothesis proposes that each plaque may be a distinct clone from a single cell, each lesion representing a benign neoplasm derived from the cell which was transformed by some agent.

Table C-1

Some Factors Which Have Been Shown To Injure
Endothelium and Increase Permeability To Lipoproteins

Clinical Condition	Substance or Physical Condition
Hypertension	Hemodynamic forces Angiotensin II
Catecholamines - Other Vasoactine Substances (Serotonin, Bradykinin)	Stress, Cigarette Smoking
Mechanical Trauma	Catheter injury
Hyperlipemia - Increased Lipoproteins (Cholesterol, Triglycerides) and free fatty acids	High Fat and Cholesterol diets Familial Hypercholesterolemia Diabetes Mellitus

Source: Modified from Wissler, R.W., Principles of the Pathogenesis of Atherosclerosis. In Baaunwald (ed.) Heart Disease, Philadelphia: W.B. Saunders, 1980, pp. 1221-1245.

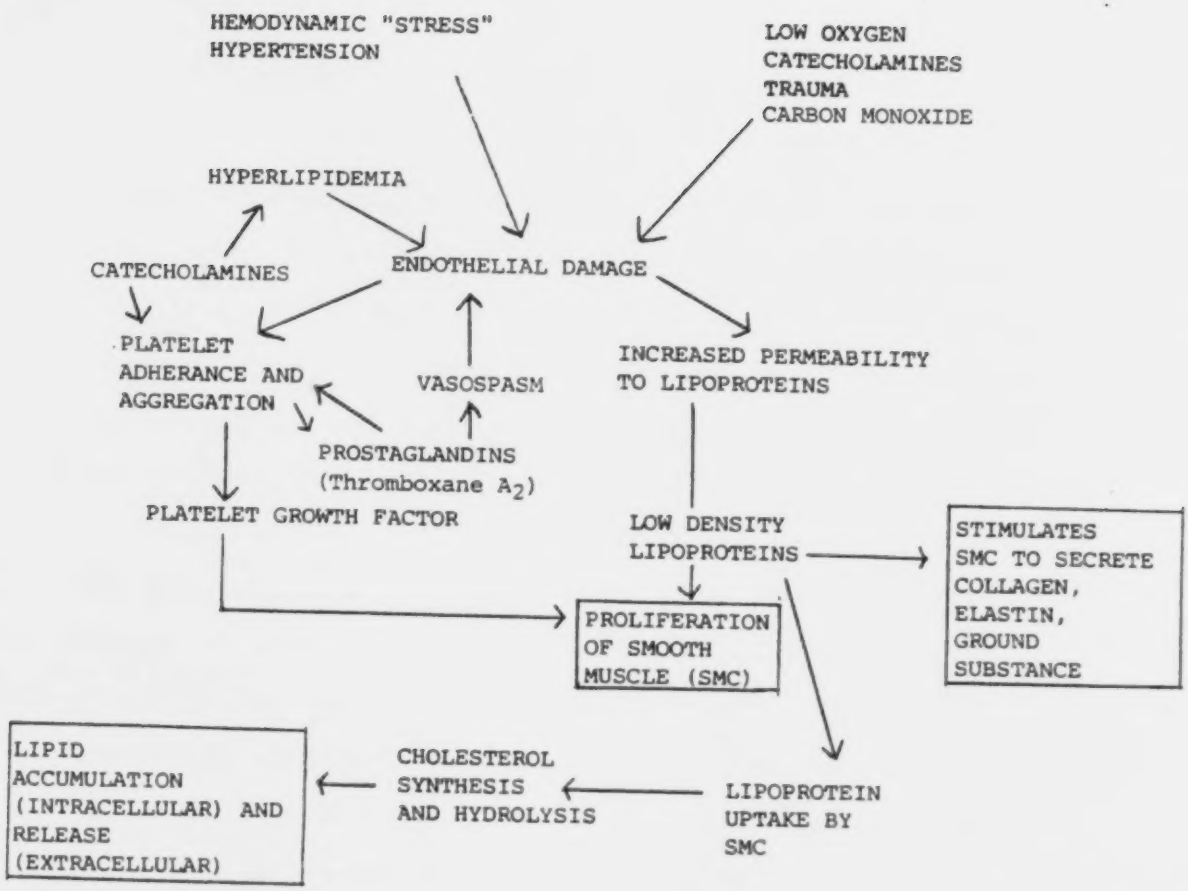


Figure C-1. Pathogenesis of Atherosclerotic Plaque
(Response to Injury Hypothesis)

Source: Modified from Kottke, B.A. and Subbiah, M.T., Pathogenesis of Atherosclerosis. Mayo Clinic Proceedings 53: 35-48, 1978

A clonal-senescence hypothesis proposes that some smooth muscle cells grow at faster rates, "wear out" more rapidly and die. As the cells die, an inhibition of smooth muscle cell proliferation and hyperplasia is lost.

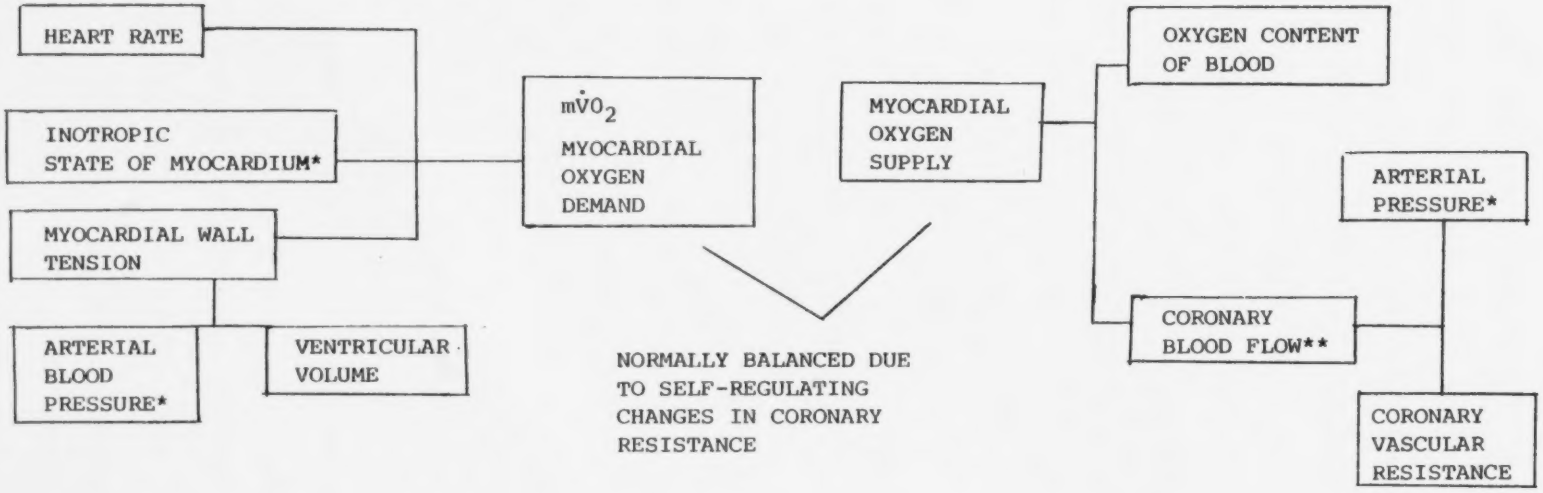
2.2 Ischemic Heart Disease (IHD)

2.2.1 Basic Dynamics

Ischemic heart disease consists of pathological disorders and clinical syndromes produced by hypoxia of the myocardium and perfusion inadequate to "wash out metabolic products". In certain situations hypoxia occurs without decreased perfusion. However, in most cases of ischemic heart disease both hypoxia and decreased perfusion occur since the major underlying lesion is limited coronary blood flow secondary to atherosclerosis of the coronary arteries.

Adequate oxygenation of the myocardium requires a balance of oxygen requirements (demand) and supply. The oxygen supply is primarily dependent on coronary blood flow which depends on the systemic blood pressure and vascular resistance. The latter is usually self-regulating. If there is an obstruction or narrowing of the coronary arteries, flow will be limited. Oxygen delivery may also be limited by the oxygen content of the blood which is determined by hemoglobin concentration and oxygenation of the blood by the lung.

There are three major determinants of myocardial oxygen consumption ($m\dot{V}O_2$). The first is the tension developed in the wall of the myocardium which is related to systemic arterial pressure and the volume of the ventricle. The inotropic state of the myocardium and the heart rate are the other two. Both are increased by increased sympathetic tone and circulating catecholamines. (Figure C-2).



*Modified by sympathetic tone or circulating catecholamines

**Limited by anatomical obstruction of coronary arteries or functional obstruction with coronary artery spasm.

Figure C-2. Major Determinents of Oxygen Demand and Supply to the Myocardium

When demand exceeds supply the myocardium becomes ischemic, producing (1) changes in myocardial function-contractility and relaxation, (2) an accumulation of metabolic products, (3) electrophysiological alterations which produce arrhythmias and electrocardiographic changes and (4) cardiac pain. If the ischemia is not relieved, cellular death occurs. IHD is due to a change in this supply and demand relationship and produces three major clinical manifestations; acute myocardial infarction (AMI), angina pectoris (AP), and sudden cardiac death (SD). Chronic congestive heart failure and cardiac arrhythmias constitute other clinical conditions which may result from ischemic heart disease. (Figure C-3).

2.2.2 Acute Myocardial Infarction (AMI)

Sudden and/or prolonged myocardial ischemic results in myocardial necrosis. This may occur when there has been a sudden change in the coronary blood supply. For many years the major proposed mechanism for this has been occlusion of a coronary artery usually at the point of an atherosclerotic plaque by a superimposed thrombosis. The role of coronary thrombosis as the major initiator of acute coronary occlusion and infarction has been questioned in the last several years. Thrombosis may be secondary to the infarction rather than the initiator. Some of the observations supporting this include (1) the occurrence of thrombus without AMI, (2) the low incidence of thrombi in sudden death, (3) the documented occurrence of AMI without thrombus, (4) higher incidence of thrombi associated with relatively large infarcts and with infarcts complicated by cardiogenic shock. Hemorrhage into the plaque causing occlusion, emboli, vasculitis, prolonged system hypotension, and spasm of the coronary artery can also interrupt or limit oxygen supply. There is growing evidence that spasm may be a precipitating factor in certain cases of myocardial infarction. Prolonged and excessive

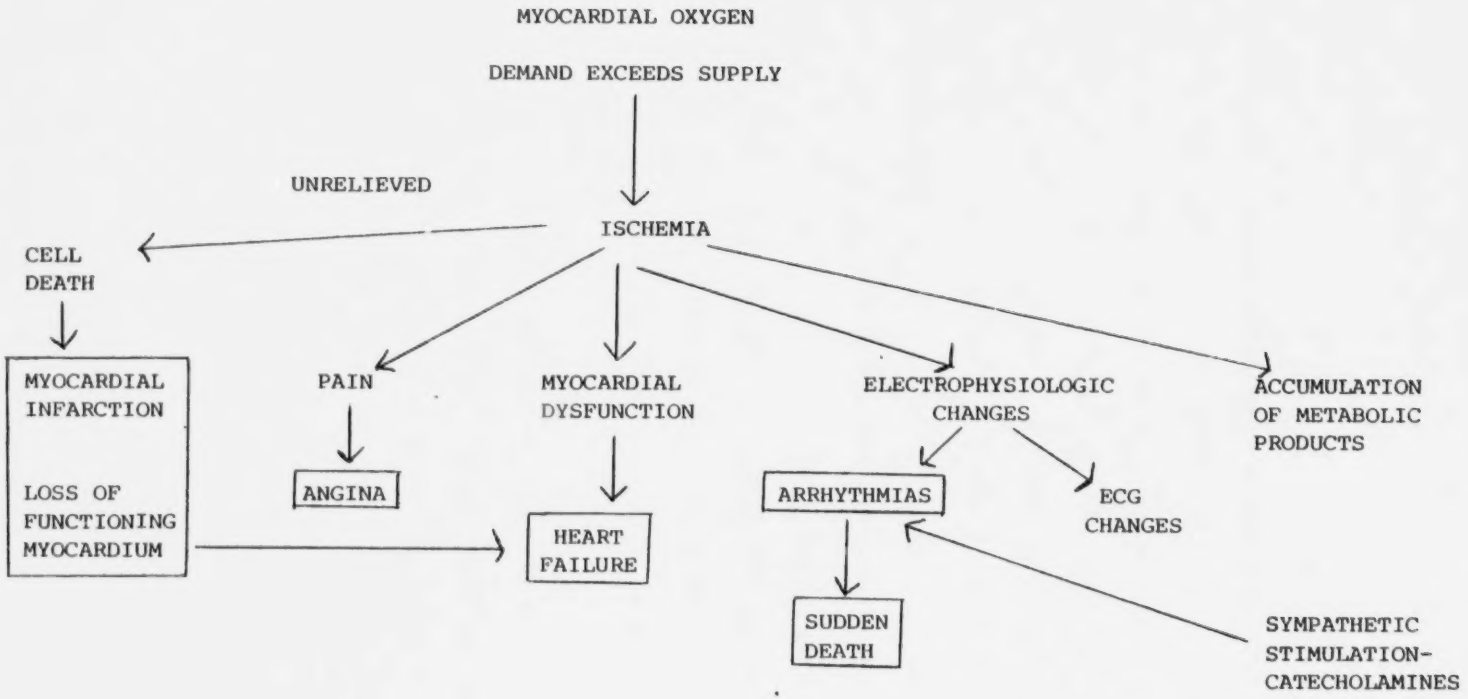


Figure C-3. Results of Myocardial Ischemia

myocardial oxygen demand in the face of limited supply may also be a precipitating event of myocardial infarction.

2.2.3 Angina Pectoris (AP)

Angina pectoris, the second major manifestation of IHD is a transient chest pain syndrome in patients with coronary artery disease who develop ischemia secondary to situations in which the demand exceeds the supply (e.g., exercise, emotion, cold environment). Ischemia is reversible when the precipitating factor is removed or therapy is instituted. In addition to classical angina pectoris there are several other recognized intermediate coronary chest pain syndromes. In the Prinzmetal variant form of angina, coronary artery spasm appears to be the precipitating event, (with or without the presence of atherosclerosis).

Factors which may play a role in coronary spasm include autonomic neural influences, circulating catecholamines, platelet aggregation, local alterations in clotting and/or fibrinolytic system and the prostaglandins system.

An interaction of platelets and prostaglandins synthesis exists but the triggering mechanism is not known. Tromboxane A_2 (TxA_2) is a potent vasoconstrictor produced by platelets during their aggretation. Another prostaglandin prostocyclin (PGI_2) produced by vessel walls is a potent vasodilator and inhibitor of platelet aggregation. Spasm, enhanced by an imbalance of TxA_2 and PGI_2, may be the initiating factor in Prinzmetal angina, AMI and sudden death.

2.2.4 Sudden Death (SD)

In most epidemiologic studies sudden death is defined as unexpected death occurring instantaneously or within 24 hours of the onset of symptoms.

Ischemia of the myocardium results in electrical instability of the heart which may lead to ventricular fibrillation, a lack of organized contraction, resulting in loss of pump function. Many clinical studies have documented that sudden instantaneous death is usually associated with ventricular fibrillation. It is also clear that the autonomic nervous system plays a major role in the electrical instability of the myocardium. Stimulation of the sympathetic and parasympathetic systems will produce cardiac arrhythmias in the absence of myocardial ischemia in both normal and abnormal hearts. Although sudden death (especially instantaneous death) is frequently equated to the presence of advanced atherosclerosis, it is not the only cause of sudden death especially those defined as death within 24 hours of the onset of symptoms. (See Table C-2).

Any study of sudden death as a health effect must carefully control for times of onset of death, unexpectedness of death, prior disease and disability, and cause of death determined by autopsy.

2.3 Stroke

Stroke is manifested by the sudden development of a neurological defect due to interruption of the blood supply to the brain or physical disruption of the brain. The brain is critically dependent on its oxygen supply and irreversible damage occurs if it is deprived of its blood supply for over 3 minutes.

There are two basic types of stroke: infarction and hemorrhage. Infarction is ischemic necrosis secondary to obstruction of the artery supplying an area of the brain. This obstruction may occur from thrombosis of an artery or embolism of thrombi (or other material such as platelets or plaque debris) from a remote site such as the heart or extracranial

Table C-2
Distribution of Sudden Deaths

	No. of Deaths	Autopsied No.	Autopsied %
Cerebrovascular Disease	99	47	47.5
Rheumatic Heart Disease	28	15	53.6
Arteriosclerotic Heart Disease	661	177	26.8
Hypertensive and Other Heart and Vascular Disease	133	68	51.1
Pneumonia	24	24	100.0
Cirrhosis	35	33	94.3
Other	97	43	44.3
Total	1077	407	37.8

Reprinted from "An Epidemiological Study of Sudden and Unexpected Deaths in Adults," Medicine 46(4):341-361, 1967, by Lewis Kuller, M.D., Abraham Lilienfeld, M.D. and Russell Fisher, M.D., by permission of The Williams & Wilkins Co., Baltimore.

vessels. Hemorrhage produces change by disruption of the tissue or exertion of pressure on the brain to produce ischemia and necrosis. Atherosclerosis is the most common underlying disease in thrombotic strokes but there are other less common causes of vascular occlusive disease in the cerebrovascular system.

Areas predisposed to atherosclerosis occur in the intracranial as well as extracranial portions of the carotid and vertebral arteries. The location of the occlusion determines the neurologic deficit and produces several major syndromes. Transient Ischemic Attacks (TIA) are transient focal neurological defects usually associated with extracranial carotid or vertebral occlusive disease. Present concepts suggest that the transient nature of these episodes are due to thromboembolism of aggregated platelets and debris from ulcerated atherosclerotic plaques. The microemboli rapidly fragment and dissolve accounting for the transient nature of the attacks.

Another major syndrome is due to occlusion of intracerebral vessels which often produces cerebral infarction. This thrombotic or embolic stroke is usually superimposed on atherosclerosis. Occlusion of the major superficial vessels produce large areas of infarction and particular clinical syndromes involving both sensory and motor systems. Occlusion of the deep penetrating vessels produce small areas of infarction (lacunar infarct) which produce more focal and limited defects of less severe nature, frequently with complete resolution. These defects may be the most common form of stroke and are almost invariably associated with hypertension.

Cerebral hemorrhage (intracerebral or parenchmyal) occurs from rupture of small penetrating arterioles usually in the presence of moderate and severe hypertension. A hematoma is produced displacing brain structures.

The hemorrhage may be massive with up to 80% mortality or small with variable recovery of the neurological defect.

Subarachnoid hemorrhage or hemorrhage into the subarachnoid space may occur from extension from a parenchymal hemorrhage, but most often is due to rupture of an aneurysm which is frequently congenital in origin. Hypertension is less often associated with this condition.

2.4 Hypertension

2.4.1 Classification and Sequelae

Hypertension is defined simply as an elevation of systolic and/or diastolic blood pressure. Diastolic hypertension may be secondary to, or a complication of other diseases. In addition, certain disease states result in an elevation of systolic blood pressure alone, a result of increased cardiac output, as is seen with arteriovenous fistula and thyrotoxicosis. Hypertension may also accompany aging with atherosclerotic changes and rigidity of the aorta and large arteries. Most hypertension is of the diastolic type with an accompanying systolic elevation. Diseases of the kidney, the endocrine system and the neurologic system may be associated with hypertension. In such cases patients are said to have secondary hypertension, some of which are curable with correction of the primary disease.

Patients who do not have an obvious reason for being hypertensive are said to have primary hypertension. It is thought that ninety-five percent of all hypertensive patients have the primary type. The most common cause of secondary hypertension is renal disease. The more common types of hypertension are listed in Table C-3.

The morbidity and mortality associated with hypertension is secondary to the effects on particular target organs, the brain, heart, kidney, vascular

TABLE C-3

TYPES OF HYPERTENSION

I. Systolic hypertension

- A. Increased cardiac output (e.g., A-V fistula, thyrotoxicosis, hyperkinetic circulation)
- B. Rigidity of aorta

II. Diastolic and systolic hypertension

- A. Primary (Essential or Idiopathic)
- B. Secondary
  - 1. Renal
    - a. Renal parenchymal disease (e.g., acute or chronic glomerulonephritis, chronic pyelonephritis, polycystic disease)
    - b. Renovascular disease
  - 2. Endocrine
    - a. Acromegaly
    - b. Hypothyroidism
    - c. Adrenal
      - 1. Cortical: (Cushing's Syndrome, Hyperaldosteronism)
      - 2. Medullary: (Pheochromocytoma)
    - d. Hypercalcemia
    - e. Exogenous (e.g., Estrogen, Glucocorticoids, Mineralocorticoids, Licorice, Sympathomimetics, Tyramine-containing foods)
  - 3. Coarctation of the aorta
  - 4. Toxemia of pregnancy
  - 5. Neurogenic

system, and the gastrointestinal tract. These effects are due to either an increased work load on an organ or to vascular changes of the small resistance vessels secondary to the elevated blood pressure, (i.e., medial hypertrophy, fibrinoid necrosis, arteriolarsclerosis). Hypertension also accelerates the atherosclerotic process in all vessels. Table C-4 lists several of the major disorders associated with hypertension according to organ and possible pathologic mechanism.

Hypertensive Heart Disease is heart disease due to the effect of sustained arterial hypertension on the heart with the development of left ventricular hypertrophy and subsequently left ventricular failure. Ischemic Heart Disease due to atherosclerosis (the development of which has been accelerated by hypertension) may accompany and complicate hypertensive heart disease.

2.4.2 Etiology of Primary Hypertension

It has been noted by Cassel that in spite of the spectacular advances in elucidating the pathophysiology of hypertension, little progress has been made in understanding its etiology. Unlike atherosclerosis, there are less clear cut risk factors associated with hypertension. There is a significant genetic predisposition to hypertension which is manifested within both families and races.

The frequency of hypertension between populations correlated fairly well with the salt intake of the population. The individual blood pressures response to salt intake may be determined by a genetic predisposition and "sensitivity" to salt. Obese persons are more likely to be hypertensive than lean persons. Obesity may be a marker of susceptibility to hypertension in a young person.

Table C-4

CLINICAL DISORDERS ASSOCIATED WITH HYPERTENSION

Target Organ	Clinical Disorders	Pathophysiologic State
Brain	Hypertensive Encephalopathy	Fibrinoid necrosis, edema, hemorrhage
	Transient Ischemic Attack	Atherosclerosis plus emboli (plaque, platelets, lipids)
	Cerebral Infarction	Atherosclerosis Thromboemboli, Thrombosis
	Parenchymal Hemorrhage	
	Subarachnoid Hemorrhage	Ruptured congenital aneurysm; Extension of parenchymal hemorrhage
Heart	Heart Failure	Increased afterload (arterial pressure) Hypertrophy; Decreased compliance; Decreased contractility
	Coronary Artery Disease	Atherosclerosis
Kidney	Excretory Renal Failure	Intimal hyperplasia and ischemia; Fibrinoid necrosis and glomerulitis
Aorta	Saccular and Fusiform Aneurysms	Atherosclerosis
	Dissecting Aneurysm	Medial degeneration
Gastrointestinal Tract	Ischemia, Infarction and Hemorrhage	Intimal Hyperplasia Fibroid necrosis Atherosclerosis and thrombosis

Source: Modified from Johnson, J.G. and Muirhead, E.E. Vascular Complications of the Hypertensive State. IN Hunt, J.C. et al., (eds.) Hypertension Update. Bloomfield, N.J.: Health Learning Systems, Inc., pp. 38-51, 1980.

2.4.3 Blood Pressure Control and Pathogenesis

The major factor in control of arterial blood pressure is a balance between cardiac output and the peripheral arteriole resistance.

BLOOD PRESSURE = CARDIAC OUTPUT x PERIPHERAL VASCULAR RESISTANCE

The major perameters which effect cardiac output and peripheral resistance are shown in Figure C-4. Heart rate is a major parameter in control of cardiac output. The other parameters listed effect venous return to the heart and stroke volume.

Arterial blood pressure is maintained in a narrow range by an active feedback regulating system. Pressure sensitive receptors (baro-receptors) located in the carotid sinus and the arch of the aorta, provide for autonomic nervous control of heart rate, strength of myocardial contraction, and venous capacitance and peripheral resistance. For example, an increase in arterial blood pressure results in stimulation of the receptors and an increase in impulses to the vasomotor center of the brain. This results in a decrease (inhibition) in sympathetic nerve impulse outflow and a concomitant increase in parasympathetic outflow of nerve impulses. The vagus nerve stimulation results in a decreased heart rate and the sympathetic nerve impulse decrease results in reduced peripheral resistance and cardiac output. Thus blood pressure returns to its normal values. It appears that for chronic hypertension to develop there must be some resetting of the baro-receptor control system which blunts the responses of this feedback system. Cerebrocortical impulses may directly stimulate the vasomotor center to increase the sympathetic nerve outflow which will raise blood pressure.

A second major control system for arterial blood pressure is related to control of blood volume as well as peripheral resistance. This system responds less rapidly than the nervous control system. This humoral system

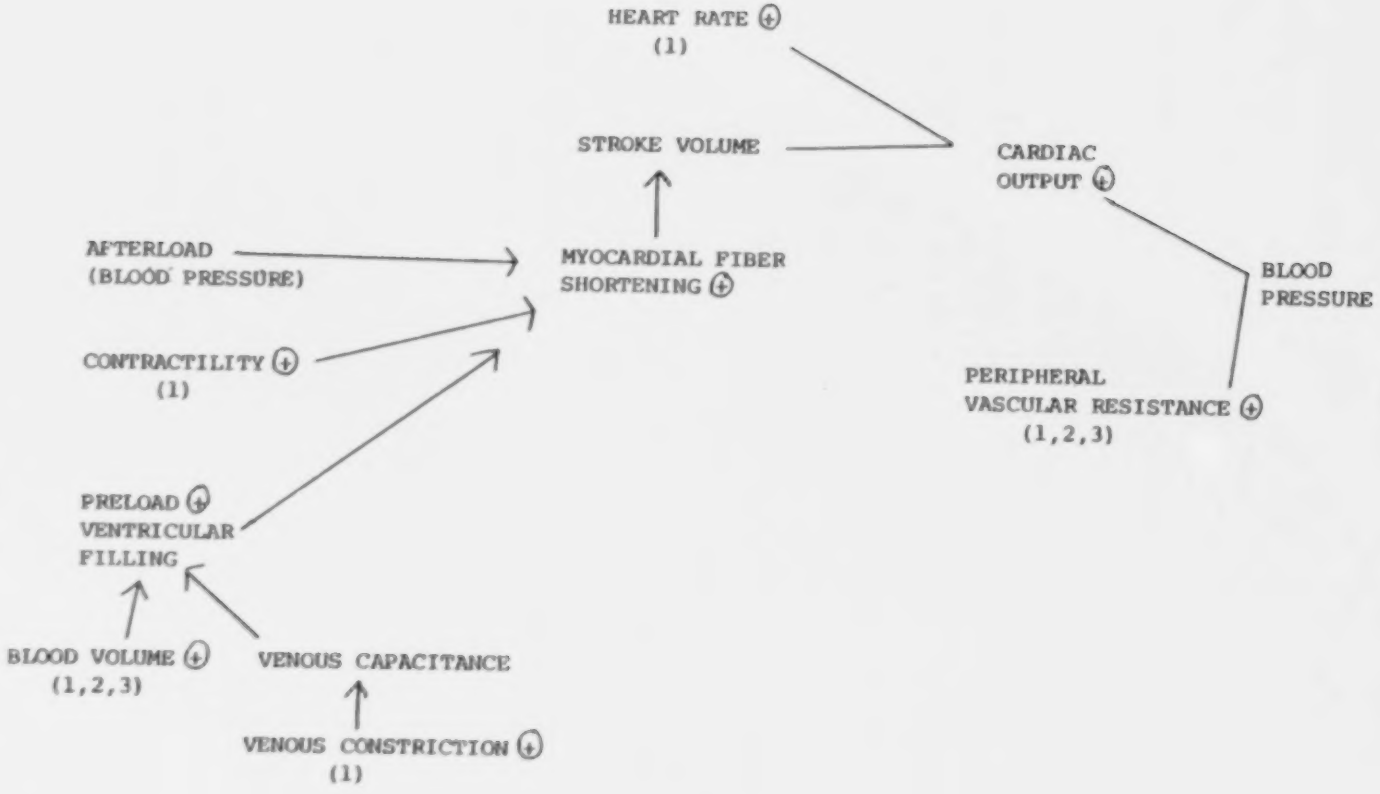


Figure C-4. Factors Influencing Cardiac Output and Peripheral Resistance

Key: ⊕ Indicates that an increase in the factor will result in an increase in blood pressure

1- Increased by stimulation of the sympathetic nervous system

2- Increased by stimulation of the Renin-Angiotensin-Aldosterone system.

3- Kallikrein-Kinin and Prostaglandin systems active - usually in depressing or counterbalancing effects of stimulation

involves the renin-angiotensin-aldosterone system. Renin release from the juxtaglomerular cells of the kidney is influenced by several parameters: (1)a decrease in blood pressure (perfusion pressure) in the afferent arteriole of the kidney; (2)decrease in sodium ion in the distal tubule of the kidney; and (3)direct stimulation of the renal sympathetic nerves. Released renin results in conversion of renin substrate in blood to angiotensin I, which is subsequently converted to angiotensin II by "converting enzymes." These enzymes are located in vessel walls and in lung tissue. Angiotensin II is a potent vasoactive substance which causes an increase in peripheral resistance. Angiotensin II elevation stimulates the secretion of the adrenal cortical hormone, aldosterone. Elevated aldosterone values produce renal sodium ion and water retention, thus blood volume is increased. While it is clear that increased renin-angiotensin II activity is a component of certain types of secondary hypertension involving the kidney, the role in chronic essential hypertension remains unknown.

Patients with essential hypertension have been characterized into three groups on the basis of renin excretion: (1)low renin, (2)normal renin, and (3)high renin. High renin hypertension accounts for 10-15% of all cases of essential hypertension.

On the basis of the renin studies in hypertension, as well as the response to therapeutic interventions, it appears that there are at least two types of essential hypertension. One being those cases in which there is a major increase in blood volume and cardiac output (volume dependent hypertension), which is associated with low or normal renin, and a second type in which there is a vasoconstrictive hypertension. This latter type is associated with normal or low blood volume and elevated serum renin. Patients with normal renin activity may have a mixed component of both volume dependent as well as vasoconstrictive

hypertension. Early in the course of the development of hypertension there is an increased cardiac output and blood volume. With longer standing hypertension there is increasing vasoconstriction, the cardiac output returns to normal, and blood volume decreases.

More recently attention has been given to other humoral systems which affect peripheral vascular resistance and the renal handling of salt. These are the prostaglandin and kallikren-kinin systems which also interact with the renin-angiotensin system. Prostaglandins are synthesized in the kidney and arterial walls. Two compounds active on vascular smooth muscles are prostacyclin, a vasodilator and thromboxane A_2, a vasoconstrictor. Prostaglandins also produce natriuresis. Renal nerve stimulation and norepinephrine as well as angiotensin II and bradykinin promotes prostaglandin synthesis.

It appears that prostaglandin synthesis in the kidney plays a role in local regulation of renal blood flow. Thus, this mechanism protects the kidney from ischemia, rather than having a major effect on peripheral resistance by release into the systemic circulation. Stimulation of the kallikren-kinin system, results in the production of bradykinin. This substance reduces peripheral resistance, and causes renal loss of sodium ion and water. This system appears to respond to stimuli similar to that described for the renin-angiotensin system. Although there is growing evidence that these systems are important in blood pressure regulation, their role in the etiology of hypertension is unknown.

A deficiency in the systems may allow a greater blood pressure response to activation of the renal angiotensin system.

The sympathetic nervous system plays a major regulating role in the maintenance of blood pressure both by direct stimulation of the cardiovascular system and by stimulation of the renin-angiotensin system. The prostaglandins

and the kallikrein-kinin systems may modify the responses of the system. Certain persons have a genetic predisposition to hypertension which may be mediated by increased sensitivity to sodium intake.

It is also evident that the feedback systems which regulate blood pressure must be reset to higher values for sustained hypertension to develop. Figure C-5 gives insight into the potentially complex interrelationship of these systems. However, for the present, we must say that the exact etiology of primary hypertension is not know.

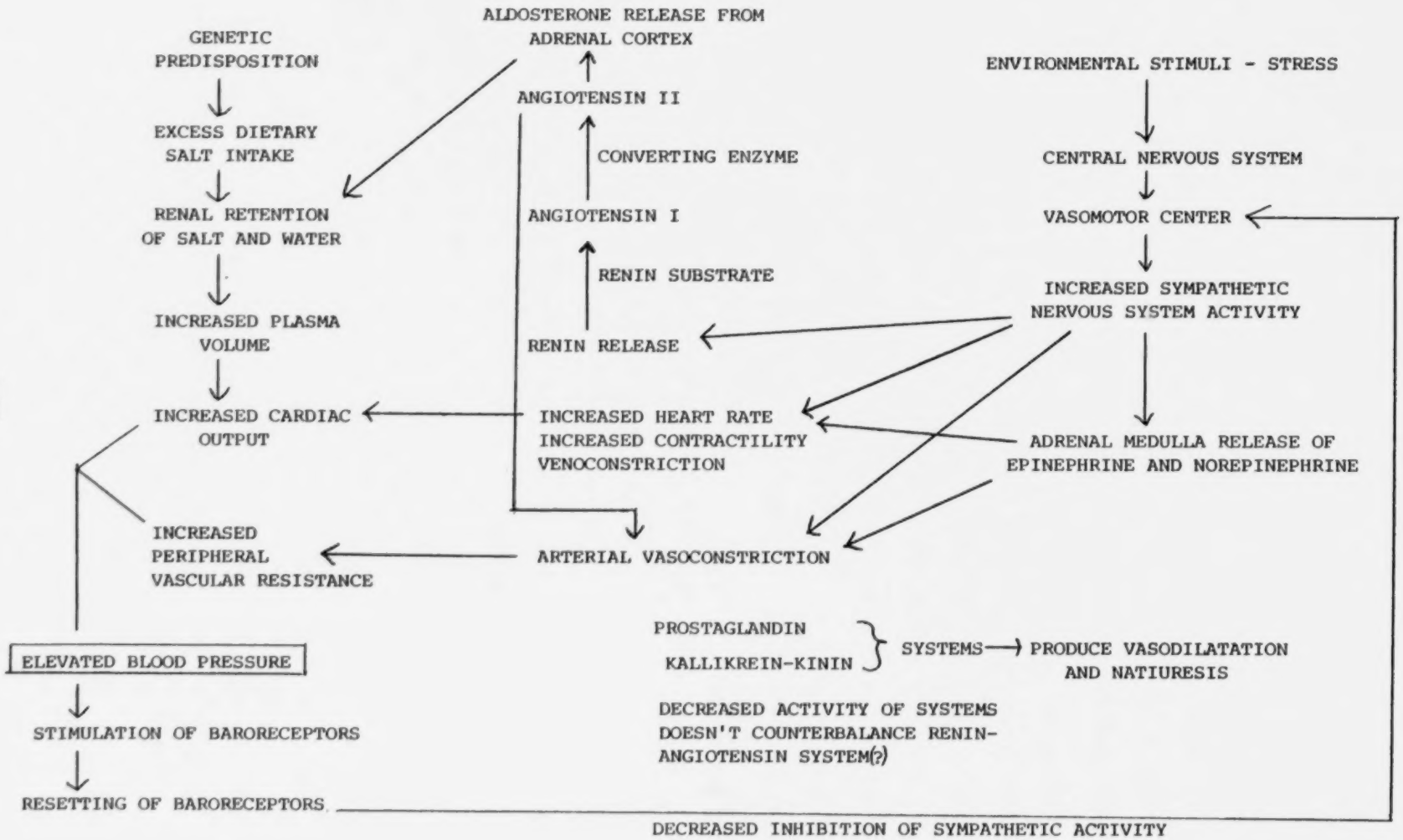


Figure C-5. Mechanisms in the Development of Essential Hypertension

3. CARDIOVASCULAR DISEASES: EPIDEMIOLOGY

There is strong evidence that cardiovascular diseases have been declining in recent years. Ischemic heart disease (IHD) and stroke mortality have markedly decreased in the last ten years. Data for the United States have shown that IHD death rates have been going down since the mid-sixties while stroke mortality seems to have been declining at least since 1940.

The decline in mortality from these diseases has been concomitant with marked changes in their treatment modes, social mores, social programs, and public health practices. These declines have not occurred evenly throughout the world, nor have the declines shown a return to rates occurring earlier in the twentieth century before the advent of the current epidemic of cardiovascular disease.

Studies in which the decrease in cardiovascular death rates have been observed have not addressed the key issue of whether mortality has declined because incidence has decreased or whether treatment has reduced case fatality or whether a combination of reduced incidence and improved treatment has reduced mortality. Figures C-6 and C-7 show mortality trends in the U.S. for IHD and strokes for whites and all other races, by sex for the period 1950-1976.

3.1 Ischemic Heart Disease

Ischemic heart disease (IHD) is generally considered to be the rubric for 1) acute myocardial infarction (AMI), (2) angina pectoris, and (3) sudden cardiac death. In light of recent developments, the term

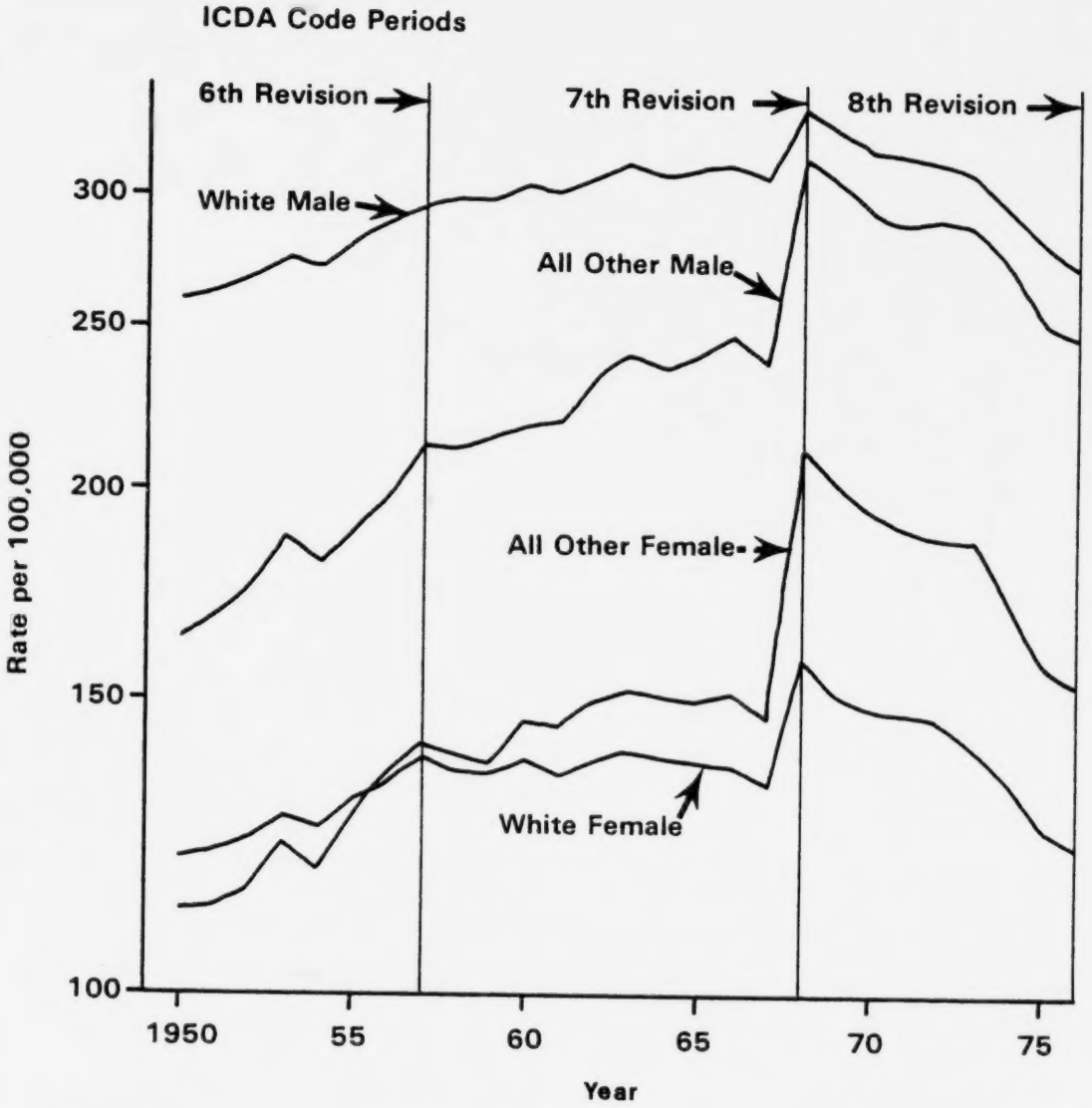


Figure C-6

Age Adjusted Death Rates for Ischemic Heart Disease, by Race and Sex: United States, 1950-1976 (Semi-log scale)

Source: National Center for Health Statistics, Chartbook for the Conference on the Decline in Coronary Heart Disease Mortality: Comparability of Cause-of-Death Statistics, Figures and Tables, and Technical Notes Describing Trends in Ischemic Heart Disease Mortality in *Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality*, edited by Havlik, J.R. and Feinleib, M. sponsored by the National Heart, Lung, and Blood Institute, NIH Publication No. 79-1610, May 1979.

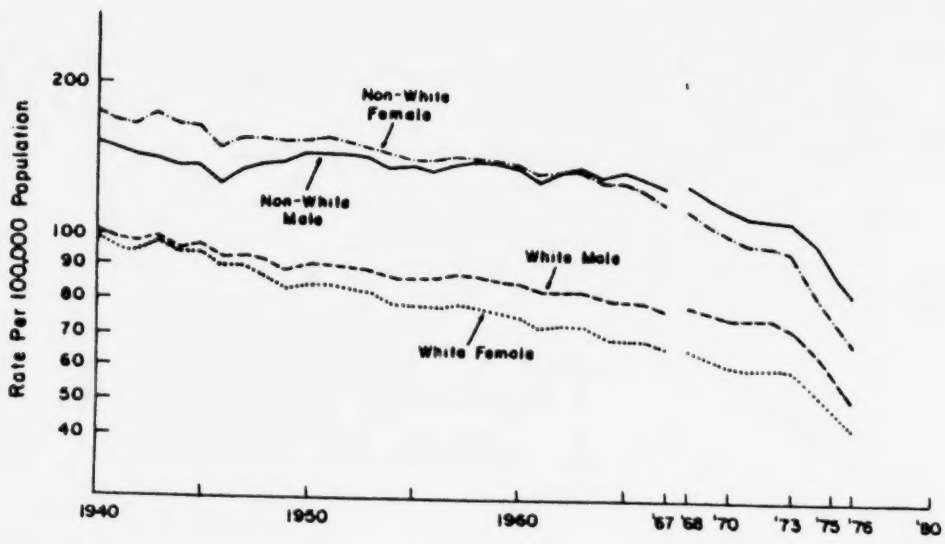


Figure C-7. Age-adjusted death rates for cerebrovascular disease by sex and race, United States, 1940-1976.

Reprinted from "A Review of Stroke Epidemiology," Epidemiologic Reviews 2:136-152, 1980, by Adrian M. Ostfeld, M.D., by permission of the Johns Hopkins University Press.

ischemic heart disease is now replacing the less descriptive coronary heart disease (CHD) identifier. IHD presently is thought to account for about one third of the deaths in the United States. Galyean (1978) estimates that more than 600,000 persons die each year from this constellation of diseases, 165,000 under the age of 65 years.

IHD mortality rates in the U.S. are next to the highest in the world, Finland having the highest and Japan the lowest rates (Stamler, 1979).

3.1.1 Acute Myocardial Infarction (AMI)

According to Willerson (1980), in almost every instance, some degree of narrowing of coronary artery luminal diameter resulting from atherosclerosis exists in persons with acute and/or old myocardial infarction.

Annual incidence of AMI as estimated from several cohort studies and one case-series study are shown in Table C-5. When age-adjusted to the same standard population, the incidence rates in the Nashville, Columbia and Framingham communities were remarkably similar. In all communities studied, white males have rates markedly above the other race and sex groups. In the three Southeastern communities (Nashville, Columbia, Charleston) white male rates were 1.75 to 3 times those of non-white males. White and non-white female rates for AMI were similar in each study area.

Table C-6 arrays the risk factors for AMI gleaned by Galyean (1978) from an extensive review of the literature. However, hypercholesterolemia, systemic arterial hypertension and cigarette smoking are generally perceived to be the key risk elements.

Sedentary activity, psychosocial stresses, elevated glucose, obesity, environmental factors, and demographic variables are thought to be secondary

Table C-5

Annual Incidence[1] of AMI in Selected Communities, by Race-Sex Groups

	White Males	Non-White Males	White Females	Non-White Females
Nashville, TN (1962-68)	6.3	2.1	1.9	1.1
Columbia, SC (1978)	7.2	4.1	2.2	1.8
Framingham, MA (1948-64)	5.7	---	1.2	---
Charleston, SC (1960-1975)	13.1	7.2	6.5	7.3

[1]Incidence Rates per 1,000 population, Nashville, Columbia, and Framingham age adjusted by direct method using Columbia metropolitan area as standard population. Charleston data only comparable across race-sex groups.

Sources for Nashville, Columbia, Framingham: Zmyslinski, Lackland, Keil Higgins, 1981

Sources for Charleston: Keil, Loadholt, Sandifer, Boyle, 1981 (in preparation).

Table C-6
Risk Factors for Ischemic Heart Disease

Age	Hemodialysis
Blood Pressure	Male sex
Cigarette smoking	Metabolic factors
Dietary factors	Diabetes Mellitus
Lipids	Gout
Sucrose	Homocystinemia
Coffee	Obesity
Water	Oral Contraceptives
Ethanol	Psychosocial factors
Environmental factors	Sedentary living
Air pollution	Viruses
Noise	

Reprinted from "Risk Factors for Coronary Heart Disease," Southern Medical Journal 71(6):694-704, 1978, by James R. Galyean, M.D., by permission of the Southern Medical Journal.

to the key three. Family history of AMI, particularly at an early age also seems to predispose one to extra risk. Data from the Charleston Heart Study (Keil, et al, 1981) suggest there may be different sets of factors for each race-sex group; that for white males, elevated cholesterol, cigarettes, and hypertension are the best predictors of AMI; for white females, hypertension and obesity; black males, cigarettes and history of diabetes; and for black females, history of diabetes seems to be the best predictor. It must be realized however that diabetes could be a marker for hypertension and elevated cholesterol. But, as Willerson (1980) points out, the clinically significant lesion of atherosclerosis is the atherosclerotic plaque.

A new concept has evolved with the evidence that coronary artery spasm may act as a pathophysiologic factor in patients with typical and atypical angina and AMI. (Oliva, 1977; El-Maraghi, 1980; Hillis, 1978; Maseri, 1978 a & b; Braunwald, 1978; Mudge, 1979). Further, recent studies suggest that sudden cardiac events and AMI are usually separate entities with differing pathogenesis, since in the majority of patients resuscitated from sudden death evidence of important AMI does not develop.

3.1.2 Angina Pectoris

Angina pectoris known since antiquity was first described by Herbeden (1802). Its original written description and prognosis continue to this day to adequately describe typical angina, its manifestations, and its pre-myocardial infarction course.

Diagnosis of angina has, without electrocardiographic or angiographic information, been completely subjective. However, Geoffrey Rose (1968) developed his Rose questionnaire which allows a more objective judgement of the presence or absence of this disease component of IHD.

Shurtleff (1970) estimates the annual incidence rates (per 10,000) of angina pectoris for white men in the Framingham study to range from 8 at age 35-44 to 27 for ages 45-54, 75 for 55-64 and down slightly to 56 for ages 65-74 years. A similar pattern was observed in the Israeli heart study which indicates a rise in incidence until age 60 years, and then a drop off (Medalie, 1976).

In a probability sampling (N=2,184) of Charleston, South Carolina residents in 1960, 2.7% of those 35 years and older reported a history of angina. This prevalence was across race/sex groups (Keil, et al, 1974).

In the five year prospective cohort study of 10,000 men in Israel, seven variables were found by univariate analysis to be significantly associated with the development of angina pectoris. They remained significant using the multivariate risk function. These seven were (1) anxiety, (2) all severe psychosocial problems, especially family problems, (3) total serum cholesterol, (4) systolic or diastolic pressure, (5) age, (6) non-specific T waves or myocardial ischemia on EKG, and (7) diabetes mellitus.

The presence of all seven risk factors (at a high level) increases the probability of angina pectoris developing in 5 years to 289 per 1,000 from 14 per 1,000 when these factors are low or absent. Anxiety and psychosocial problems were among the strongest predictors in both univariate and multivariate analyses.

Over the years, many patients presenting with chest pains did not meet the criteria for typical angina, i.e., pain did not come on with exertion and was not relieved by rest. Many of these chest pains were thought to be of psychosomatic origin. In recent years, Prinzmetal's angina has been defined, elucidated, and associated with coronary artery spasm, a transient event which may cause intermittent chest pain or at its extreme

be a prime precipitant of acute myocardial infarction or sudden cardiac death.

3.1.3 Sudden Cardiac Death

Sudden cardiac death which claims 400,000 lives annually or about 60% of all IHD fatalities has been recognized since the beginning of recorded history (Lown, 1979).

Sudden cardiac death has two aspects: (1) an acute, precipitating factor and (2) a chronic predisposition of electrical instability of the myocardium. Ventricular premature contractions (VPC) constitute risk factors for ventricular fibrillations and sudden cardiac death according to Lown (1970, 1971) and it is estimated that 90% of patients with IHD exhibit ectopic activity (Ryan, et al, 1975 and Lown, et al, 1975). Lown suggests that VPC's may represent the trigger for repetitive activity leading to ventricular fibrillation or VPC's may be an innoccuous concomitant in the electrically unstable heart. In the first case, suppression may prove protective; in the second, the underlying electrophysiologic derangement may continue even though ectopic activity is controlled. He estimates that the population with myocardial electrical instability (from which sudden cardiac death victims are drawn) probably includes several million people.

In Seattle over a period of 6 years, there have been 346 long term survivors out of 1710 episodes of ventricular fibrillation. Recurrent cardiac arrest has resulted in a 26% mortality at 1 year and 36% at 2 years (Cobb, et al, 1978).

Numerous clinical and epidemiological studies have demonstrated that individuals who experienced sudden cardiac death have certain symptoms in the days or weeks prior to the sudden death. The most common symptoms

include marked increase in fatigue out of proportion to the usual activities, chest pain and shortness of breath (Feinlieb, et al, 1975). Sudden and unexpected deaths due to arteriosclerotic heart disease occur almost exclusively to individuals who have extensive coronary artery stenosis (Perper, 1975). Sudden death victims generally have evidence of old infarcts and perhaps LVH. The key predictive factors are the extent of the IHD and LVH (Oberman, et al, 1972 and Detre, et al, 1978).

Lown (1975) has noted that sudden death is not the end stage of severe heart disease. The mechanism is ventricular fibrillation and certain types of VPC's may reflect the presence of electrical instability and risk of sudden death. The precipitants of these arrhythmias may be related to change in CNS activity, secondary to social and environmental stresses. Greene, et al (1972) noted that sudden death may occur in basically depressed men with high physiological coronary disease risk factors, who for some reason experience high arousal. Friedman, et al (1973) suggest that prodromata occur in the sudden death, but are rare among the instantaneous deaths (within seconds).

The consistency of the fatigue syndrome (i.e., from study to study and for different race and sex groups) suggests that this syndrome is real and an important premonitory symptom of sudden death. Kuller (1978a) hypothesizes that fatigue may be related to decreased left ventricular function or alternately, it may represent a manifestation of depression.

Of 87 sudden deaths reported on by Reichenbach, et al, (1977), seven were found not to have extensive coronary artery disease at postmortem. Thus, it may be conjectured that 7/87 (8%) may have been electrical and the balance 80/87 (92%) may have been electrical and/or thrombus mediated AMI's.

As demonstrated by Rahe and Lind (1971) and by Theorell, et al, (1975), it is clear that some life change and the individual responses to them may be regarded as prodromata of sudden death. A case control study by Cottington, et al, (1980) reveals that relative to matched controls, cases were six times as likely to have experienced the death of a significant other person in their life within the previous six months. They were no more likely to have experienced changes in living conditions or work than the controls. The sample of sudden deaths included 81 Caucasian women ages 25-64 years.

Kuller (1978a) believes that individuals who die suddenly of arteriosclerotic heart disease have a high frequency of prodromal symptoms in the days or weeks prior to death. Qualitatively, they are similar to those reported by patients prior to an AMI. He thinks this prodromata may be related to: (1) true change in symtomatology secondary to chronic underlying CV disease, (2) acute pathophysiologic changes which are a harbinger of sudden death or AMI, or (3) pathophysiologic responses related in some way to the social and physical environment.

3.1.4 Atherogenesis

The obvious key to the greatest proportion of ischemic heart disease is atherosclerosis as has been demonstrated by autopsy and surgical studies. Epidemiologic studies indicate that lipids balance account for a large part of the risk in ischemic heart disease and probably the principal element in atherogenesis. Blood pressure, stress, smoking cigarettes, lack of exercise, personality type, alcohol and other factors have also been implicated as substantive variables which influence the process of atherogenesis.

Kuller (1976) has characterized cardiovascular disease as a continuum beginning with atherogenesis which starts with fatty streak, proceeding to fibrous plaque, and then advancing to coronary artery stenosis. It is at this point that the cardiovascular system is primed for a precipitant of manifest clinical diseases. Indeed, it might be conjectured, that these may simply be a continued insult from the "classic" risk factors or their interactions to trigger the coronary artery spasm.

Stamler (1979) believes that the epidemic of premature IHD in the U.S. and other western industrialized countries is a result of modern lifestyles and the risk factors related to them. He implicates habitual eating patterns high in cholesterol, saturated fats, and calories as the primary cause of the epidemic.

3.1.5 Cholesterol and Lipids

McGill (1979) attributes the discovery of cholesterol to Michel Eugene Cherreul of France who in 1812 first differentiated between saponifiable and nonsaponifiable lipids. Adolf Windaus of Freiburg began work on the structure of cholesterol in 1903 and the correct structure was finally established in 1932 (Fieser, 1950).

Stamler (1979) considers the extensive epidemiologic data on the relationship of "rich diet, hypercholesterolemia, hypertension, and cigarette smoking" to risk of IHD, to meet the esential criteria for demonstrating that the associations are indicative of an etiological relationship because

(1) the associations are strong;

(2) the associations are graded in nature;

(3) the associations have the necessary temporal relationships in that the risk factors precede the disease;

(4) the associations are generally consistent in multiple studies;

(5) the associations are independent;

(6) there is powerful and accurate predictive capacity; i.e., application of data on risk factors from one population yields good prediction of IHD in another population and the individuals in it; and

(7) the data are coherent in that the epidemiologic data are consistent with findings from other research methods, and reasonable pathogenic mechanisms are known.

However, he cites as evidence for the primacy of cholesterol, epidemiological and animal studies which show a high correlation (r = .725) between per capita availability of calories from principal animal sources and CHD mortality rates for men (Figure C-8). He also cites data from Armstrong, (1974, 1976), showing that an increase in plasma cholesterol supervenes when cholesterol is added to the diet of monkeys at levels less than or equal to those frequently consumed by Americans. After 18 months on this diet, arterial intimal thickness was present in all cholesterol fed groups, generally proportional to the increase in dietary and plasma cholesterol, (Figure C-9).

Hypertension, a condition not productive of atherosclerosis by itself has been shown to accelerate and intensity atherogenesis in cholesterol-fat fed animals according to Katz (1958), Stamler (1967), and Pick, et al, (1974). Stamler has discussed a number of human studies which also point to hypertension and smoking as key but secondary risk factors. He cites Paffenbarger's work (1966) which showed that a single examination of blood pressure, weight, and smoking taken in the teens was predictive of IHD risk 20, 30 and 40 years later. Stamler (1979) also emphasizes that data from international living population and autopsy studies and animal experimental data all show that when the habitual diet is low in cholesterol and saturated fats, severe

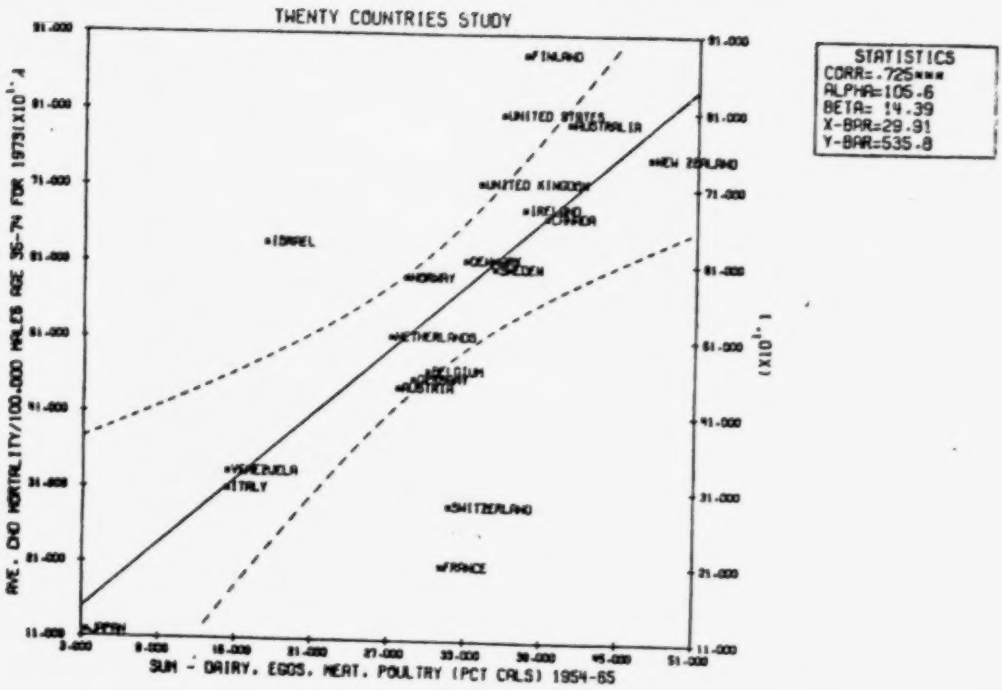


Figure C-8. Relationship between average per capita availability of calories from principal animal sources, expressed as percent of total calories, and age standardized 1973 coronary heart disease mortality rates for men. Twenty Countries Study.

Reprinted from "Research Related to Risk Factors," Circulation 60(7):1575-1587, 1979, by Jeremiah Stamler, M.D., by permission of the American Heart Association, Inc.

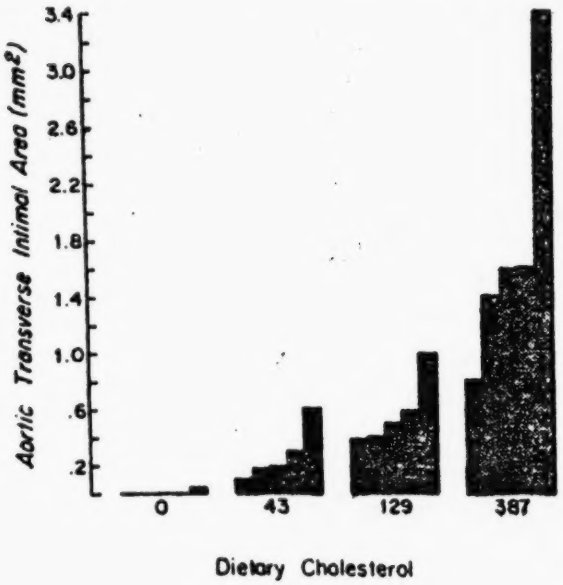


Figure C-9. Relation of dietary cholesterol to aortic intimal thickening, measured as area in transverse microscopic sections. Shown are the average areas from preselected sites in individual monkeys, five animals per dietary group.

Reprinted from "Regression of Atherosclerosis," Atherosclerosis Reviews 1:137-182, 1976, by Mark L. Armstrong, M.D., by permission of Raven Press.

Cited in Stamler, Jeremiah: Research Related to Risk Factors. Circulation 60(7):1577, 1979.

atherosclerosis and its clinical consequences, particularly premature IHD are rare even when important factors as hypertension and cigarette smoking are present.

According to McGill (1979) several factors account for the intensive interest and investigation of the link between human atherosclerotic heart disease and cholesterol. The rapid increase in frequency of IHD in the 1940's and 1950's in the U.S. led to more intensive investigation of its etiology. The observation that cardiovascular disease mortality declined in Western Europe during WW II when butter and eggs were scarse cast suspicion on these dietary components as possible causes of atherosclerosis. Then the demonstration in the early fifties that the probability of developing IHD could be predicted by serum cholesterol levels in "normal" persons focused attention on factors that affected serum cholesterol concentrations.

McGill has grouped the epidemiological studies and given a critical review to each. These are summarized in the following paragraphs.

World War II Studies: The validity of the association between cardiovascular mortality and dietary restrictions can be criticized because many other changes such as cigarette smoking were taking place and the changes have not been subject to detailed analysis. During WW II the general reduction in caloric intake may have caused weight losses which reduced hypertension and diabetes. No specific data implicated cholesterol.

National or Regional Population Studies: Despite the many comparisons of arteriosclerotic heart disease mortality among nations, states, and regions, few have attempted to relate mortality to dietary cholesterol or to egg consumption. The few that have done so form a strong association between mortality and cholesterol on the basis of simple correlation coefficients. When many other interrelated variables were considered in

computing a partial correlation coefficient the association with dietary cholesterol or egg consumption diminished markedly, or disappeared. Therefore, McGill thinks these associations cannot be considered evidence for a causal relationship.

Small Group Studies: In contrast to the national or regional studies in which comparisons were made on the basis of mortality rates, small groups usually have been compared on the basis of serum cholesterol concentrations. However, problems with the presence of many interrelated variables also confound the findings. McGill concludes that most results of comparisons of smaller groups show an association between dietary cholesterol and serum cholesterol but provide no conclusive proof of a causal relationship.

Studies Based on Individual Values: McGill reviewed some 14 reports in this category which usually tested associations between dietary cholesterol and serum cholesterol. Three of them tested the association of dietary cholesterol and IHD and one examined the association with coronary artery atherosclerotic lesions. He states that these papers show little or no association of dietary cholesterol with either serum cholesterol, coronary atherosclerosis or IHD.

McGill concludes there are three problems with the observational (epidemiological) studies: (1) confounding of all observational studies by multiple independent variables; (2) the subtle but fundamental difference between group correlations and individual correlations. McGill quotes Robinson (1950) in stating that ecological correlations cannot be used as substitutes for individual correlations. The author suggests that group correlations must be interpreted as describing groups and not describing the responses of individuals to specific environmental agents;

and, (3) the effects of within and between subject variation and methodological error on the suspected relationships.

For the period up to 1979 (McGill, 1979) also reviewed experimental studies in humans and found nearly 50 reports which he summarized as followed:

1950-1959: 12 studies showed a variable but weak relationship between dietary and serum cholesterol.

1960-1969: 21 studies presented evidence that dietary cholesterol influences serum cholesterol but to a lesser degree than saturation of dietary fatty acids.

1970-1979: 14 investigations showed varied results but a better study (Mattson, et al, 1972) showed a linear relationship between dietary cholesterol and serum cholesterol within the range of 0-317 mg/1000 kcal per day.

He points out that numerous controlled experiments have demonstrated that the average serum cholesterol concentration of adults increases with increasing dietary cholesterol when the total intake is in the range of 0-600 mg/day. Estimates of the average increase in serum cholesterol concentration range from 3-12 mg/dl per 100 mg of cholesterol per 1000 kcal. Dietary cholesterol above about 600 mg/day produces no additional effect in most persons. The response tends to be greater if dietary cholesterol is combined with saturated fats.

In examining others' work, McGill suggests the possibility that dietary cholesterol could affect atherogenesis without changing the serum cholesterol. Mahley's work (1978) reported that the addition of 4-5 eggs per day to the diet of eleven free-living men and women increased HDL subfractions. The increased activity of HDL appears regardless of the effect of the eggs on plasma cholesterol concentration. The observation that egg supplementation alters the lipoprotein profile as in particular the properties of HDL independently of serum cholesterol offers a new potential mechanism that needs further exploration and confirmation.

Mann, et al, (1964) has reported that Maisi (in Africa) have low serum cholesterol, little or no advanced atherosclerosis and practically no atherosclerotic disease in spite of diets high in cholesterol and animal fat. This author thinks it conceivable that a large proportion may possess resistance to dietary cholesterol but concludes that more accurate measurement of dietary intake and confirmation of their resistance to dietary cholesterol are necessary before they are cited as showing unusual resistance to dietary cholesterol.

Finally, McGill, after examining early review articles on cholesterol states that none provide a comprehensive and critical review of whether dietary cholesterol has an independent effect on serum cholesterol concentration, atherosclerosis, or atherosclerotic heart disease. The key conclusion of these reviews follows:

Keys (1957)	Animals are much more sensitive to dietary cholesterol than humans. For all practical purposes, the dietary cholesterol variable may be disregarded.
Ahrens (1957)	Serum cholesterol levels were independent of dietary cholesterol.
Katz (1958)	Cholesterol and fats alone were ineffective in inducing hypercholesterolemia in animals but the combination of the two was effective.
Connor (1970)	Dietary cholesterol in amounts up to 110 mg/day did not effect serum cholesterol. From 110 to 600 mg/day serum cholesterol increased; above 300 there was a plateauing effect.

McGill thinks there is evidence that serum cholesterol can be reduced by the elimination of eggs from the diet. However, because there are many low responders, much cholesterol is derived from other sources, and other dietary factors (saturated fats) affect serum cholesterol. Thus, any reduction in serum cholesterol must be accomplished by changes in a variety of dietary components.

Twenty years ago Shekelle, et al (1981), evaluted diet, serum cholesterol and other variables in 1900 middle aged men and repeated the evaluation one year later. No suggestions for treatment were made. Vital status was determined at the 20th anniversary of the initial exam. Scores summarizing each participant's dietary intake of cholesterol, saturated fatty acids and polyunsaturated fatty acids were calculated according to the formulas of Keys (1965) and Hegsted (1965) and their coworkers. These authors report that the two scores were highly correlated and results were similar for both. They showed a positive association between diet score and serum cholesterol concentration of the initial examination, a positive association between change in diet score and change in serum cholesterol concentration from the initial to the second examination, and a positive association prospectively between mean baseline diet score and the 19-year risk of death from IHD. These associations persisted after adjustment for potentially confounding factors. Their results support the conclusion that lipid composition of the diet affects serum cholesterol concentration and risk of coronary mortality in middle aged American men.

Although there may be contrasting evidence (some authors say little evidence) for dietary cholesterol affecting serum cholesterol, there still may be other environmental stressors, in addition to genetic traits, which exert an influence on serum cholesterol components.

3.2 Stroke

Every year nearly 400,000 people in the U.S. become stroke victims. According to Toole (1980) approximately 40% of these die within a month and at least 2/3 of the survivors have some degree of permanent disability. At the present time, the population of the U.S. includes 2½ million disabled

survivors. The cost of care and loss of earnings is estimated by Toole to be 9½ billion dollars annually.

For the period of 1967-73 Massey (1979) has shown that Japan had the highest stroke rates (males 250 and females 150 per 100,000 per year), while Poland and Mexico had the lowest rates averaging about 50 per 100,000 per year for both sexes. In this tabulation the U.S. ranked 23 of 28 countries reviewed.

In Rochester, Minnesota (Matsumoto, 1973) prevalence of stroke was shown to be about three times the annual incidence. These findings are summarized in Table C-7. Kuller (1978b) states that the accuracy of stroke mortality and morbidity statistics within the same community will generally be quite similar. He reports that in most U.S. communities nearly all stroke victims are hospitalized except those in the oldest age group and patients with transient cerebral ischemia. Kuller also cautions one to be sure that patients are residents of the same area as those comprising the denominator.

Schoenberg (1979) has addressed the diagnostic concerns when dealing with cerebrovascular disease as involving three levels of diagnosis (1) examination of constellation of signs and symptoms (2) determining the type of disease, and (3) delineating the extent, location and multiplicity of the vascular lesion.

Kurtzke (1976) has reported the types of stroke to occur in the following proportions - atherothrombotic brain infarction, 69%; cerebral embolus, 12%; subarachnoid hemorrhage, 8%; other types including intra-cerebral hemorrhage, 11%. Results from the Framingham Study as published by Kannel (1975) have been remarkably similar. Kannel considered the sequellae among 309 patients who experienced stroke during a 22 year follow-up period.

Table C-7

Incidence[1] and Prevalence[2] of Stroke for Males and Females by Age Group, Rochester, Minnesota, 1973

Age Group	Males		Females	
	Incidence	Prevalence	Incidence	Prevalence
45-54	1.8	7.0	1.4	3.7
55-64	4.0	15.1	3.5	16.0
65-74	12.7	33.5	9.6	36.7
75-84	22.6	77.8	22.2	67.1

[1]Incidence per 1,000 per year

[2]Prevalence per 1,000 per year

Source: Abstracted from Matsumoto, N, Whisnant, J.P., Kurland, L.T. and Okazaki, H., Stroke 4: 20-29, 1973.
Cited in Kuller, L.H.: Epidemiology of Stroke. Advances in Neurology 9, pp. 285-286, 1978.

One hundred ninety died and of those surviving (119), 56 had motor deficits. Eighty-four percent of the survivors lived at home, 9% were in rest homes or nursing homes, and 7% were in chronic disease hospitals.

Availability of new antihypertensive drugs is cited by Ostfeld (1980) as a key reason that there has been a decline in stroke since 1950. He also states that decrease in mortality may be attributed to health education and to improved methods of treatment. He also presents evidence of a decline in incidence because the proportion of persons in the Kaiser - Permanente Medical Plan who were hospitalized for stroke declined in the period 1971-77.

Three reasons are given by Ostfeld for the pre-1950 decline in stroke mortality rates: (1) artifactual reduction because of an aging population from 1940 when the U.S. population was 132 million and 6.8% were over 65 to 1970 when the population was 204 million, 9.8% being over 65. (By taking the number of stroke deaths for each age group in years after 1940, but age adjusting to the 1940 population, stroke rates are artificially reduced by a small amount.); (2) improved diagnosis and (3) black migrants to the North took on the blood pressure characteristics of the Urban North (which were presumably lower than in the South at that time).

There is increasing evidence that high blood pressure may cause strokes. The VA studies (1967, 1970) have demonstrated that lowering BP can reduce stroke incidence and the High Blood Pressure Detection Follow-up Program (1979) provides evidence that rigorous treatment of hypertension reduces stroke mortality.

Ostfeld (1980) considers blood pressure, diabetes, pre-existing CHD (RR=3) and TIA's to be leading risk factors for stroke, but other factors thought to be associated include obesity, cigarette smoking, LVH, triglycerides, cholesterol.

Friedman (1968) has also suggested that cardiac arrthymias may be related to risk of brain infarction. Atrial fibrillation is associated with a substantial increase in embolic and thrombotic strokes even when cardiac impairment and high blood pressure are considered.

Other correlates of stroke are black race and being female. Low temperatures, low altitudes, and water hardness have also been implicated as increasing the risk of the disease.

3.3 Hypertension

3.3.1 Epidemiologic Definitions

Hypertension is a blood pressure level above which there is liable to be excess morbidity or mortality for an individual. Hypertension is a blood pressure above that required for normal function (i.e., perfusion of organs and tissues). And, another investigator (Wagner, 1974) has defined hypertension as that blood pressure below which therapy does more harm than good, meaning that medication side effects and their accompanying risk exceed the risks associated with high blood pressure.

Pickering (1974) insists that blood pressure is a series of continuous and normally distributed values and infers that hypertension is a misnomer for the reasons indicated in the preceding paragraph. For, contrary to Platt's (1959) theory of two classes of blood pressure (normotension and hypertension), Pickering (1974) asserts that the relationship between arterial pressure and mortality is quantitative; the higher the pressure, the worse the prognosis.

3.3.2 Clinical Definitions

Physicians generally like to consider patients as (a) normotensive, (b) those with labile hypertension, i.e., extremely transient "elevations" of pressure, (c) those with benign hypertension, i.e., fixed elevated pressure with slight anatomical change and (d) those with accelerated or malignant hypertension involving physiologic and anatomic pathology. Hypertension may, also, be viewed as primary in which the etiology is uncertain, or secondary to other diseases such as pheochromocytoma, Cushing's disease or other assorted nephritic diseases (Ledingham, 1971; Laragh, 1974). Clinically, hypertension, at various times, may be considered to be a disease, a sign, risk factor or a precursor of disease.

Mahomed (1881) first observed that elevation in blood pressure may either precede or follow renal disease and proposed the concept that "what is the cause in one case may be the result in another". A number of investigators (von Basch, 1893; Huchard, 1889 and others) confirmed this hypothesis; and in 1914, Volhard and Fahr differentiated nephritis from nephrosis (i.e., caused by primary hypertension) and classified arteriosclerotic diseases causing hypertension into benign and malignant phases of essential hypertension.

More recently, subclassification of essential hypertension based on plasma renin, angiotensin and aldosterone was made by Laragh, et al 1974), Oparil and Haber (1974) and others. Schanberg, et al (1974) have also suggested identification based on plasma levels of dopamine beta hydroxylase.

Currently operating hypertension clinics usually have, as their minimal admission standard, persistent (three weekly determinations) arterial pressures ranging from 150-170 mm Hg systolic and 95-100 mm Hg diastolic

plus the criterion of no demonstrable cause. Although hypertensive patients are frequently asymptomatic, typical symptoms may include early morning occipital headache and unsteadiness (not true vertigo). Additionally, there may be signs of changes in the arterioles of the optic fundi or other end organ damage, particularly within the kidney. As regards symptoms, however, Pickering (1974) suggests that most symptomatology is iatrogenic. He cites Stewart's work (1953) which found that of 104 patients who were unaware of elevated arterial pressure, 87 had no headache; of 96 who had been told they were hypertensive, only 27 had not complained of headache. In Ayman and Pratt's study (1931), the chief early complaint of their hypertensive patients were headache (72%), pain (67%) and nervousness (67%). The frequency of these symptoms was similar to those found in 50 psychoneurotic subjects with normal blood pressure.

3.3.3 Measurement of Blood Pressure

Direct methods of measuring pressure require invasive and complicated techniques not generally applicable to epidemiologic studies nor to clinical practice. Thus, the traditional, and widely used, indirect method of measuring systolic and diastolic arterial pressure involves the sphygmomanometer introduced by Riva-Rocci in 1896.

Variations in blood pressure readings may be due to true variations (induced by emotional state, physical activity, position, temperature, etc.), instrument error or observer error (McCaughan, 1966). Bevan, et al (1969) demonstrated this by attaching to himself and others an automatic measuring device which recorded blood pressure over a continuous 24 hour period. The author, who by most criteria would be considered normotensive, had pressures which ranged from 55/30 mm Hg during sleep to 150/70 during

periods of (1) a painful stimulus (a pin stick in his posterior), (2) coitus, and (3) his helping to get his children off to school and as he began to work. His blood pressure averaged about 95/55 for several hours after lunch, rose somewhat between 5 and 8 p.m., but returned to 95/55 and remained at this level until he retired. According to Rose, et al (1964) the observer may introduce error due to the following factors: (1) mental concentration and reaction time, (2) hearing acuity, (3) confusion of auditory and visual cues, (4) interpretation of sound, (5) rates of inflation and deflation, (6) reading of moving column, (7) preference of certain terminal digits, (8) bias. Thus, the measurement of blood pressure, which appears to be a simple matter, may be subject to large errors or variations. Special consideration must be given to reducing or standardizing these differences in epidemiologic studies, since one must recognize that a blood pressure measurement, at best, is a sampling of one of many possible levels.

Design of epidemiologic studies of blood pressure must, therefore, address itself to standardization of instrumentation, observer(s), and participants. Comstock (1957), found in his studies in Muscogee County, Georgia, that blood pressure taken at home tended to be lower than those taken elsewhere; although he determined that the overall differences were not marked. He compared home and office blood pressures of 93 individuals in his study and found that, on the average, systolic pressure was 1.9 mm Hg higher and diastolic pressure, 3.9 mm Hg higher in the office setting than at home. For males, the office readings were lower than the field readings; whereas, for females, the reverse was true. Comstock says that since the field readings were made by female nurses and the office ones by male physicians, the blood pressure of the subjects may be higher when the examiner is of the opposite sex.

Pickering (1974) says that although the arterial pressure, as measured in office or clinic, by no means represents the arterial pressure at other times of the day or night, it is, in fact, a value which is reasonably replicable, provided that the usual precautions are taken of ensuring that the patient is comfortable, resting, quiet and at ease.

3.3.4 Distribution and Patterns by Age, Race, Sex and Residence

Blood pressure measurements are approximately normally and unimodally distributed if the sampling is representative of the population, as numerous publications by Pickering (1968, 1974), Hamilton et al (1954), and others have adequately demonstrated. Figure C-10, a frequency polygon of the blood pressure of Charleston County residents in 1960, further demonstrates this thesis. Sir Robert Platt's (1959) arguments for a bimodal distribution (representing normotensive and hypertensive states) have been put to rest, if not dismissed.

Numerous studies (Borhani and Hechter, 1964; Franklin, et al, 1973; Hamilton, et al, 1954; Scotch, et al, 1961; Klein, et al, 1973) have shown that mean blood pressure generally increases with age although the diastolic component usually tends to level off about age 50 and may actually show a slight decrease after this age. While the above referenced studies have been cross sectional in nature, cohort studies (Borhani and Hechter, 1964 and Kannel and Gordon, 1970) reveal a similar pattern. Studies among aboriginal peoples in Ponape (Murrill, 1949) and West China (Morse, et al, 1937) indicate that, in the groups observed, blood pressure may have remained constant as age increased. As one compares these primitive groups with more modern or Westernized peoples in England, India or the United States, the differences in both systolic and diastolic blood pressures are

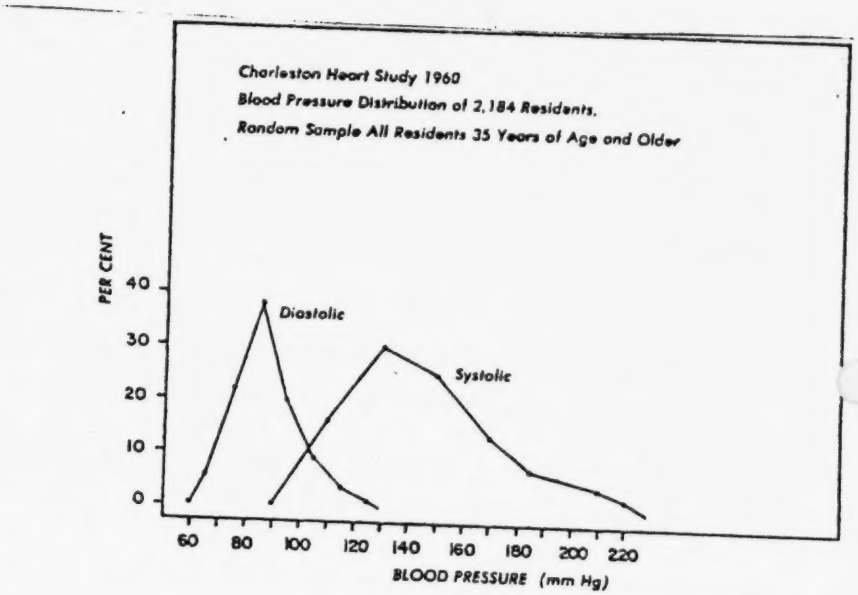


Figure C-10. Frequency Polygon of Blood Pressure in Charleston County, S.C. Residents 1960.

remarkable (Figure C-11). These differences in blood pressure might reflect cultural dissimilarity or differences in genetic stock; i.e., these isolated groups, which have minimal racial admixture, may possess unique anatomical or physiological traits which do not require blood pressure elevation for optimal performance. Geography may serve to explain some of the blood pressure differences.

Disregarding the unusual populations of the world, it can be generalized that average arterial pressure rises with age--that for systolic pressure, the growth curve is steep, but for diastolic pressure, there is generally slight deviation from linearity.

According to Pickering (1974), hypertension is more prevalent and severe in blacks than in whites. The National Health Survey of 1960 (1966) found a blood pressure of either 160 systolic or 95 mm Hg diastolic or higher in 27 percent of black adults as compared to 14 percent of white adults. Thus, the prevalence of hypertension may be deduced to be twice as high in blacks as in whites in the United States. Examination of these data also show that the racial difference seems to be accentuated in the Southeastern counties, v.i.z., Evans, Muskogee and Charleston, as compared to the United States as a whole.

Gillum (1979) presents the chronology of the epidemiology hypertension in blacks and reports that data began to emerge in the 1930's suggesting higher blood pressure levels in blacks in selected populations (Adams, 1932). According to him, it was Comstock with data from the Muskogee County Georgia Study in 1957 (Comstock, 1957) who firmly established black-white differences in a biracial community using standardized methods. Since that time their findings have been replicated in numerous surveys in the U.S. and in the West Indies. However, population-based data on blood pressure from the

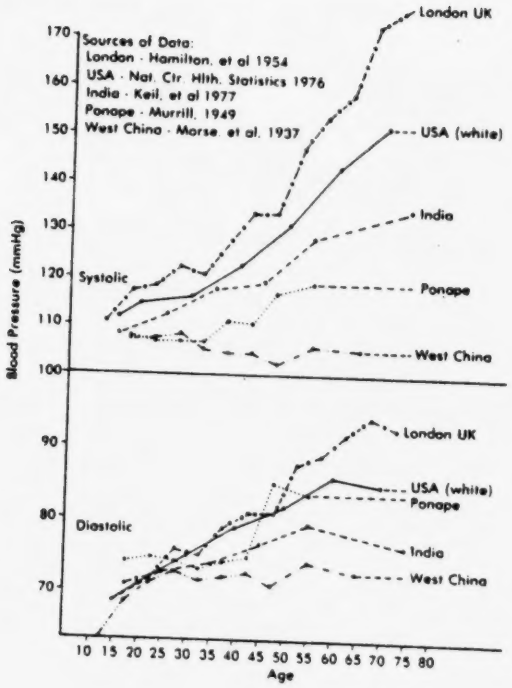


Figure C-11. Arterial blood pressure by age of selected primitive developing and modern populations (all females except West China, sex not specified).

Reprinted from "Prevalence of Hypertension in Females of Punjab State, India: Relationships with Age, Residence, Heart Rate, Occupation, and Obesity," Human Biology 49(4):641-650, 1977, by Julian E. Keil and Betty Cowan, by permission of the Wayne State University Press. Copyright 1977 Wayne State University Press, Detroit, Michigan 48202.

many countries in Africa show variable results with regard to interracial comparisons (Epstein, 1967; Akinkughe, 1972; Bays, 1953; and Kean (1949). Several investigators (Harburg, 1973; Boyle, 1970; Keil, 1977; and Tyroler, 1978) have attempted to use skin color and blood groups as genetic markers to study black-white pressure differences. Initial studies by Boyle (1970) from Charleston, South Carolina indicated that darker skin color is related to higher blood pressure among blacks. However, in later reports when social class was controlled for, this apparent effect of skin color disappeared (Keil, 1977, 1981). No correlation between BP and degree of racial admixture was found in northeast Brazil (Krieger, 1965).

Thus, there is little hard evidence from studies of skin color on blood groups to support or refute the hypothesis that black-white differences in BP arise from single or multiple genes, although it is clear from family studies of BP that genetic factors are important within each group.

Several studies (Hamilton, et al, 1954 and Masters, et al, 1950) in the early 1950s indicated that average systolic and diastolic pressures, when adjusted for age, differ in the two sexes. Those cited show females with higher systolic levels after about age 30. Diastolic pressures were higher in women than in men at all ages; the differences being very small in the youngest subjects and, thereafter, increasing steadily.

Studies conducted in 1960 in the United States have shown fairly consistent sex differences in blood pressure patterns similar to the earlier studies with sex differences being greatest in the blacks of Evans and Charleston counties.

Sex differences merit further evaluation and detailed study, if for no other reason than to explain the paradox of generally higher blood pressures

in females, yet substantially lower probability of coronary heart disease for which elevated pressure is considered to be a prime risk factor.

Some studies have shown rural-urban differences in mortality and morbidity, with the rural areas declared to be the healthier environment. Unpublished blood pressure measurements by residence for white and black males of Charleston County in 1960 presents only equivocal evidence (Keil, et al, 1975).

Abrahams (1960) has reported arterial pressures in Nigeria, one of the countries of West Africa which was the general area of origin of the Southeastern blacks. While the pattern of blood pressure change with age in the Nigerian study is similar to that of the United States, Evans County and Charleston County, the absolute levels of blood pressure in Nigerian blacks are markedly below levels of North American blacks.

3.3.5 Risks Associated with Hypertension

At least since Janeway's work in 1913, it has been known that patients with elevated blood pressure tend to die prematurely. Stated another way by Pickering (1974), the higher the arterial pressure, the worse the prognosis.

Insurance companies (although dealing with a selected population) may provide some of the better data available about the sequellae of hypertension. The Metropolitan Life Insurance Company reports confirm Pickering's hypothesis with the following findings. Men, age 35, who have blood pressures of less than 130/90 have a life expectancy of 41½ years which is reduced to 25 years as the pressure levels increase to 150/100; this decrement represents a 40% decrease in life span. This risk of 40% reduction in life span continues in males until age 55 when it moderates

to about 25%. In females, the decrease in life expectancy with increase in blood pressure (≤130/90 to 150/100) are markedly lower: 22% reduction at age 45 and 15% at age 55.

Lew (1974), of the Metropolitan Life Insurance Company, reports that blood pressures 10-15 mm under average, i.e., below 110 mm systolic and below 70 mm diastolic, are clearly optimal insofar as longevity is concerned.

Sequellae of persistent high blood pressure may be considered of two types, (1) direct organ damage and (2) indirect effects on the cardiovascular or other systems.

Direct Effects: These include end organ damage including nephroses and retinal lesions (Pickering, 1968). Another direct organ effect is considered to be left ventricular hypertrophy (Gordon and Kannel, 1972). While these direct effects appear obvious, they are no less important than more subtle ones.

Indirect Effects: The role of hypertension, in cardiovascular diseases particularly, has been intensely investigated during the last score of years. Its final rank and role in the genesis of ischemic heart disease and stroke may come only with reports from intervention trials in which modification of risks are followed by reduction in subsequent morbidity and mortality. Preliminary results from intervention trials (HDFP) showed a 17% reduction in all cause mortality resulting from a treatment protocol (HDFP, 1979).

Hypertension is considered to be one of the prime risk factors for ischemic heart disease, atherosclerotic brain infarction and intermittent claudication (Gordon and Kannel, 1972; Heyman, et al, 1971; Tyroler, et al, 1971; Kleinbaum, et al, 1971; and Kannel, 1971). That these

diseases are the leading cause of death in the United States (Chapman, 1967), in addition to their morbid consequences, is reason alone for intensive investigations into the etiology of hypertension.

Borhani, et al (1963) found that the higher the systolic or diastolic blood pressure had been among San Francisco longshoremen in 1951, the greater the risk of mortality during the ensuing ten years.

Within the study population from Peoples Gas Company of Chicago (Stamler, 1967), IHD incidence was 4.1 times as high with diastolic blood pressures of 80-89 mm Hg as with pressures less than 80 mm Hg, and 8.2 times as high with diastolic pressures of 95 mm Hg or more as with diastolic pressures less than 80 mm Hg. Risks with elevated systolic pressure were somewhat less: 2.5 times greater with systolic pressures of 140-149 as compared with a systolic level of less than 130; the risk increased to 3.1 when pressures were in the range of 150-159 when compared with those less than 130.

The Framingham Study (Kannel and Gordon, 1970) found hypertensives (systolic $\geq$160 and diastolic $\geq$95) at 4.5 times the risk of CHD at those classified as normotensive ($\leq$140/$\leq$90).

According to Page and Sidd (1973), risks associated with elevated blood pressure that came from Framingham were related to the pressure at entry into the study and the study participant's physician may have instituted treatment for some of them. Thus, if hypertension in these subjects has been modified by therapy in the interviewing years, then either treatment has been ineffective in reducing incidence of vascular disease or the risk of vascular disease has been underestimated.

Epidemiologic studies over the past decade have repeatedly stressed that hypertension is one of the "big three" risk factors for heart

attacks and sudden death. A recent summary of the evidence by Hollander (1973) stated, "The results of a number of epidemiological studies indicate that the risk of every manifestation of coronary heart disease, including angina, coronary insufficiency, myocardial infarction and sudden death, is significantly related to the antecedent level of both systolic and diastolic blood pressure." Hollander also stated that "it is not clear that hypertension, per se, in the absence of other atherogenic factors, can cause atherosclerosis," and he concluded that the vascular effects of hypertension might not be reversed by treatment of the high blood pressure.

Tyroler, et al (1971) also call attention to the fact that in none of the population studies has there been found a critical level of blood pressure above which middle-aged American men are at risk and below which they are free from the development of CHD.

3.3.6 Possible Etiology

The scientific literature abounds with theses which purport to give the cause of hypertension. Yet Pickering (1968) still speaks today for the scientific community as he wrote in 1960: "We do not know precisely (the cause). Certainly no specific fault has been identified and I am personally doubtful if one exists. But going further back we can assign roles to inheritance, which influences pressure at any age, and environment, which influences the rate of rise with age. And this is natural because, in one way at least, aging represents a cumulative effect of environmental influences."

And, Miall (1971) suggests that familial factors account for only a third of the variance of systolic pressure and a fifth of that of diastolic. Non-familial environment factors, most of which remain to be detected,

presumably account for the remainder. The major factors which have been explored as etiological are dietary factors or habits, geographical factors and chemical, physical factors.

The evidence relating salt to human hypertension is indirect and derives from three sources: (1) effects of salt restriction, (2) effects of salt elimination by diuretics, and (3) correlation between salt intake and hypertension (Dahl, 1972).

Interest in the connection between salt and hypertension was heightened somewhat about 1959 with the introduction of thiazide diuretics. Dahl (1972) contends that the effectiveness of diuretic therapy in lowering blood pressure allowed clinicians to realize that most of their hypertensive patients had not been on low sodium diets.

After comparing demographic, social and economic data with diseases involving hypertension, Jenkins, et al (1979) found that low occupational status and low education may be the most potent statistically of all the community predictors of excess hypertensive mortality.

Haynes, et al (1978) found few consistent associations between psychosocial stress measures of personality type, sociocultural mobility, situational stress, or somatic strain and levels of blood pressure or cholesterol.

According to Pickering (1968), there is a definite correlation between blood pressure and the relation of body weight to height. He cites the results of two studies to reinforce this viewpoint: (1) reduction in weight by dieting may produce considerable fall of arterial pressure when it is initially high, (2) the percentage of persons having blood pressures 20 mm Hg or more above the norm for their age, increases more rapidly with

age in the group that is 20% or more overweight than in those whose weight is within 5% of the average.

More recently, Tyroler, et al (1974) reported the seven year experience of an Evans County, Georgia, population and demonstrated that being overweight is associated with both increased prevalence and incidence of high blood pressure. Further, their work showed an association of weight change with blood pressure change.

A previous section demonstrated dissimilarities in blood pressures in various geographical locations and, in part, ascribed the differences to degree of civilization. We will now discuss specific elements of location which impinge on blood pressure.

Climate - Most reports on the effects of temperature and barometric pressure appear to be anecdotal. However, Alexander (1974) indicates that most studies of the hemodynamic effects of cold while performed in the resting state have shown an increase in arterial pressure. Doyle and Lovell (1961) found that European Australians of long residence in tropical Australia had higher pressures than those in temperate Australia. However, Takahashi (1967) considered that coldness might be one of the causes of hypertension, especially in Japan, where mortality from cerebrovascular disease is highly concentrated in the Northeastern part of the island. In 1957 he had found that persons who either had no stove in winter or had a stove five years or less had an average elevation of 11 mm of systolic pressure in winter than in summer. Those who had heat in their homes for over six years had only minimal and non-significant elevations, presumably because of adaptation mechanisms. As regards barometric pressure or altitude, Fejfar (1967) reports that high arterial pressures

are rare at high altitudes but admits that reliable epidemiologic data are not available.

Trace Metals and Drinking Water - Schroeder (1960, 1969a & 1969b) in the U.S. and Kobayashi (1957) in Japan did some of the original work which created interest in the relationship between health and mineral characteristics of local water supplies. Numerous other investigations followed, mostly of an ecologic nature. Many of these studies found an inverse association between mortality, in particular death rates from cardiovascular disease, and the hardness of local drinking water. Kobayashi, a Japanese agricultural chemist, had in 1957 found an association between stroke death rates and the acidity of water. Schroeder had a grant to investigate CV disease in the orient in 1957 and while there, was given access to the stroke-water quality data by Kobayashi.

On his return to the U.S. Schroeder sought to confirm Kobayashi's findings. Shroeder found, for the period 1949-1951 significant negative correlations between water hardness and death which ranged from -.31 for IHD; -.37 for all cause mortality; -.33 for stroke, and -.56 for all cardiovascular diseases.

In the years since these studies, numerous authors and committees reviewed the water story. Some (Shaper, 1974 and Hudson, 1976) were sufficiently convinced of the relationship between hardness and disease that they recommended action with respect to water treatment. Others equivocated, one author felt the association between water hardness and CV disease to be spurious. Others suggested that

some trace elements leached from the distribution system might be the cause.

According to Comstock (1979), most of the studies reported, used correlation coefficients to measure association rather than the regression coefficient. The correlation coefficient is affected much more by chance variation that the regression coefficient, which can be attenuated only by variations in the independent variable. Thus, the correlation coefficient gives no indication of the magnitude of effect. It is possible to get near perfect correlation of two variables even when the dependent variable changes little, if at all.

The majority of comparisons within major national subdivisions such as states or provinces support the possibility that soft water is associated with increased risk of dying from CV disease, but studies from smaller geographical areas have not been supportive of this hypothesis, according to Comstock.

It hardly seems that water hardness, per se, would be related to disease. It may be an excess of a toxic factor or deficiency of an essential one, however Sharrett (1979) who has reviewed this literature concludes that available geographic studies relating water quality to mortality rates have not provided consistent evidence regarding the effects of elements found in drinking water on the cardiovascular system.

Smoking - Borhani and Hechter (1964) found that both systolic and diastolic blood pressures were higher in San Francisco longshoremen who never

smoked than in those who were cigarette smokers. Pickering (1968) had reported similar findings in the literature. Dilation of vessels may be a partial explanation for this finding.

Link with Air Pollution - Jacobs and Langdoc (1972), using total particulates as an index of pollution, has incriminated air pollutants as the cause of increased cardiovascular-related deaths. Another author (Carroll, 1969) has also shown a statistical correlation between air-borne cadmium and prevalence of cardiovascular disease in 19 metropolitan areas. Both of these studies have used suspect epidemiolog[illegible]ethods. Lead has also been associated with elevation of blood pressure (Crepet, et al, 1956; Hsu, et al, 1957; Beevers, et al, 1980) but this may be due to kidney damage and thus producing a secondary hypertension, although in the Beevers report there was no association between blood lead and kidney function.

Birth Control Hormones - Several studies (Duke, 1975) have shown blood pressure elevations among users of birth control pills.

Recognized Disease - The prevalence of hypertension is greater in diabetics and is one of the well recognized sequellae of this disease. Barrett-Connor, et al (1981) found that of 3,456 residents surveyed in Rancho Bernardo, California between the ages of 50 and 79 years that there was an association between diabetes and hypertension in both men and women of all ages. They report that diabetes and hypertension are linked only partially by obesity and that some of the excess risk of IHD in diabetics is probably due to hypertension.

Unrecognized Disease - Several studies (Pickering, 1968) have reported increased urine proteins and uricemia among certain hypertensives.

A long time concern of renologists has been that essential hypertension, or a portion of it, may actually be secondary hypertension.

3.4 Risk Factors

3.4.1 Smoking

A number of reports (Doll and Peto, 1976; Reid, et al, 1976; U.S. Surgeon General, 1979) have shown lower IHD rates for nonsmokers. Although the relative risk of IHD given a history of cigarette smoking is modest, i.e. about 1.8 to 2. Doll, et al (1976) considers that the excess mortality from IHD in cigarette smokers is probably wholly or partly attributable to the habit. In the Charleston Heart Study (Keil, et al, 1981) cigarette smoking contributed significantly to the prediction of AMI in white and black males, but no such relationship was evident in white or black females.

Seltzer (1980), however, points out that it is reasonable to believe that stopping smoking does not reduce the risk of IHD, and that there is no established proof that cigarette smoking is causally related to IHD. He also emphasizes that after years of search and experimentation the mechanisms by which smoking might enhance manifestations of IHD have not been satisfactorily established.

3.4.2 Alcohol

According to Evans, et al (1980) several epidemiologic studies have presented evidence that men who consume small to moderate amounts of alcohol daily have a decreased risk of IHD. Their own study (Hennekens, et al, 1979) of 586 white men who died from IHD and an equal number of matched controls found that those drinkers who consumed two ounces or

less of alcohol per day had a significantly lower risk of IHD as compared to nondrinkers. As compared to nondrinkers the relative risk of death from IHD for light to moderate beer drinkers was 0.3, for wine drinkers 0.3 and for liquor drinkers, it was 0.2.

Evans, et al (1980) think that the biologic basis for the effect of alcohol on IHD may involve changes in lipids, alteration of platelet aggregation, modification of behavior patterns, and effect on life events.

3.4.3 Oral Contraceptives

Kreuger, et al (1980) examined the role of oral contraceptives (OC's) in fatal myocardial infarction and found slight evidence against the use of OC's. However, when the analysis was restricted to white AMI cases of a definite nature, and controls, who had no contraindications to OC use, users of OC's were estimated to be at about four times the risk of nonusers for fatal AMI's.

In 26 women discharged from a hospital with a diagnosis of acute myocardial infarction, who were otherwise healthy and potentially child bearing compared with 59 control women, Jick, et al (1978) found the relative risk estimate of AMI to be 14, given a recent history of oral contraceptive use.

Petitti, et al (1979) investigated the relation in women of various factors to risk of myocardial infarction, subarachnoid, hemorrhage, other strokes, and venous thromboembolism. Smoking significantly increased the risk (RR = 3-5) of all four diseases, whereas oral contraceptive use was associated with an increase only in risk of subarachnoid hemorrhage (RR = 6.5) and venous thromboembolism (RR = 7.6). Cigarette

smoking was overwhelmingly the most important risk factor for vascular disease in women.

3.4.4 Obesity

According to Stamler, et al (1978), the association of overweight with elevated blood pressure has been frequently noted. They report that in the Community Hypertension Evaluation Clinic screening of more than 1 million people, the group classifying itself as overweight had prevalence rates of hypertension 50% to 300% higher than other screenees. The frequency of hypertension in overweight persons aged 20 to 39 years was double that of normal weight and triple that of underweight persons. Among those aged 40 to 64 years, the overweight group had a 50% higher hypertension prevalence rate than the normal-weight group and 100% higher than the underweight group.

Patel, et al (1980) have shown from autopsied cases (25-64 years of age) in Orleans Parish that there is an inverse association between smoking habit and obesity, but a direct correlation between smoking habit and atherosclerosis. Positive though weak associations for measures of atherosclerosis with adipose thickness were found among whites but not among blacks. The authors suggest that obesity itself is not atherogenic but that it is related to one or more atherogenic agents that affect aortas and coronary arteries differentially and that are more intensive among whites than blacks.

3.4.5 Physical Activity

The role of physical activity as a coronary risk factor has been debated for a long time and opinions have contrasted due to the difficulties

of classifying single individuals as more or less active and to the confounding effects between habitual physical activity and some risk factors (Menotti and Puddu, 1979). Menotti and Puddu studied a cohort of 172,459 males, aged 20-64 and employed by the Italian railroad system. The overall crude mortality was 56.6 per 1000 in ten years and no significant differences were found between men in sedentary, moderate, and heavy work. Age corrected death rates for AMI and sudden cardiac death were substantially different in the three activity groups. The age corrected rates per 1000 in ten years were 14.2, 12.6, and 7.6 for sedentary, moderate, and heavy work respectively. The authors report that all differences were statistically significant.

Noakes and Opie (1979) consider that running by itself does not give absolute protection from coronary artery disease, but that it encourages a life style associated with low coronary risk.

3.4.6 Environment

The American Heart Association Task Force Report on the Impact of the Environment on Cardiovascular Disease (Harlan, et al, 1961) broadly considers that environmental hazards comprise both factors of the ambient environment and aspects of environment that are personally controlled.

The report gives examples of ambient hazards as contaminants of air, water, and food and occupational risks that cannot be controlled by the worker. Aspects of environment under personal control include cigarette smoking, various drugs, and a variety of health habits such as physical activity.

According to the authors, personal environment factors are important risk factors in the development of cardiovascular disease and based on

present knowledge appear to make greater contributions to disease development and progression than do general environmental factors.

Of the ambient hazards in the environment, the Task Force Report advocates that probably noise and physical and psychosocial stresses warrant the most attention. Further research in the areas of water hardness, trace elements (particularly magnesium) and occupational exposures are still considered desirable.

3.4.7 Stress

Stress is an imprecise term that is used to describe a force or influences that disrupts the usual physical or psychological state according to Harlan (1981). The definitions, scope, and use of the term are diverse, but we will consider stress in the light of three major influences, namely social class, life events, and personality type. Each of these three components may influence the other or interact with it to cause a positive or negative stress.

3.4.8 Social Class

Social class (SES) has been defined by Green (1970) as the relative position of a person or family in a hierachy which maximally reflects differences in behavior. Persons of a given social status are expected by their peers to behave in a given way that is complying to a social norm and thereby tend toward a statistically expected level of behavior. Thus, SES approximates the position of a person with regard to one of the frames of reference people employ to place one another, namely socio-economic level, social class participation and reputation and family or individual life styles. Social classes indexed by SES may then influence

if not dictate his physical, chemical, and psychosocial environment. Each of these may provide support or stress to his well-being. More specifically, social class has been thought by Kaplan (1971, 1975) and others (Cassel, 1975) Syme, et al, 1974, 1975) to measure or tap life styles which may involve life stresses, powerlessness, difficulties of adaptation, status ambiguity, lack of support mechanisms or how one perceives his life role and judges how if effects his security. Henry and Cassel (1969) postulate that repeated arousal of one's "defense-alarm" system may be an important tie to stimulation of vascular, autonomic and hormonal function. Repeated stimulation may then carry one to continued vasoconstriction because of catecholamine release, leading to increased renin release, thence to the cycle of angiotensin and adosterone secretion, salt and water retention and speculatively to essential hypertension (Cassel, 1975).

Additionally, social class may influence an individual's diet in ways which may have an effect on his weight or in a manner not yet sorted out by the chemists or physiologists. Social class may also be indicative of a person's residence, neighborhood, or work environment which may contain varying physical or chemical insults. The hostility of an environment may take the form of fear of physical violence or less direct things such as climate, polluted air, water, soil or food and disease.

Life style components which may be influenced by socio-economic status may also include the number of inhabitants within a residence, transportation available to work, pleasure, emergencies; religion and club memberships, health care, alcohol and tobacco use, family size and circle of acquaintances, marital status, lack of creditor pressure, and recreational opportunities.

The use of social class as a variable of concerns is easily rationalized. Even if physical and chemical causes of hypertension are identified, social class may provide the link between an individual and such etiology for social class summarizes an area of life styles, diet, mobility, and preventive health behavior.

Antonovsky (1968), after reviewing some 56 studies comparing cardiovascular morbidity and mortality with social class, reached three conclusions: (1) the perception by the medical profession of a direct class gradient with mortality is not supported by the data, (2) the majority of the studies do show class differences which are substantial. There often seem to be a curvilinear relationship between class and disease suggesting that social class is a highly important variable and (3) there may be a secular trend because more and more of the recent studies (i.e., post 1950) report no clear class gradient. Antonovsky considers class as a zeroing in variable and thinks that even if there is a secular trend with etiologic factors of disease becoming more equally distributed among different social classes, there may be an increasing emergence of an inverse gradient with regard to mortality. This is based on the premise that medical care is an intervening variable between disease and its consequences. Even if classes do not differ on the incidence of disease, they may well, given differential medical care, differ on disease mortality. Social class is usually measured by considering education, income, and occupation.

The association between four year mortality and socioeconomic indicators was studied by Holme, et al (1980) in all Oslo, Norway men aged 40-49 invited to a screening program for cardiovascular disease and in a healthy subgroup of participating men free of cardiovascular disease and diabetes at screening. They found that the lowest social class exhibited a much

higher total mortality than the other classes. This was pronounced for a variety of causes of death, such as cancer of the lung, accidents, homocide and coronary heart disease.

The findings of a five year prospective survey of the relation between occupation, education, and IHD carried out among 270,000 men employed by the Bell System throughout the continental U.S. was reported by Hinkle, et al (1968). They found that men who attain the highest levels of management as a group do not have a higher risk of IHD than men who remain at lower levels. There was no evidence that men who have high levels of responsbility or who have been promoted rapidly or frequently have any added risk of IHD.

Haynes and Feinlieb (1980) examined the responses to a psychosocial questionnaire which had been administered between 1965 and 1967 to 350 housewives, 387 women working outside the home for over one-and-one-half years, and 580 men participating in the Framingham Heart Study. Regardless of employment status, women reported significantly more symptoms of emotional distress than men. Women, working outside the home and men were more likely to report Type A behavior, ambitiousness and marital disagreements than were housewives. Working women did not have significantly higher incidence rates of IHD than housewives, however, IHD rates were almost twice as great among women holding clerical jobs as compared to housewives. Among working women, clerical workers who had children and were married to blue collar workers were at highest risk of developing IHD.

3.4.9 Life Events

Holmes and Rahe (1967) developed the concept that life changes are associated with illness onset. They developed the social readjustment rating scale in order to quantify the amount of psychosocial readjustment

required to cope with some 40 different life events. According to them, however, (Theorell, 1979) the life change measurement has proved inefficient in the prediction of myocardial infarction.

In a comparison of 120 patients admitted with unequivocal MI and 40 patients admitted to coronary care but rapidly discharged without a diagnosis of MI or other serious illness, there were no differences in life event frequency (Byrne and Whyte, 1980). But, patients with MI interpreted their life events as being particularly emotionally distressing. Another group (Suls, et al, 1979) report that Type A's report the occurrence of more life events than B's and that life events seen as undesirable were positively correlated with increased distress for Type A's.

Benson, et al (1978) believe that epidemiologic and physiologic evidence strongly suggest that stressful circumstances which require behavioral adjustment may lead to hypertension. The fact that hypertension can be treated by a behavioral intervention, the relaxation response, provides strong support to this concept, according to Benson.

3.4.10 Personality Type

Coronary prone behavior patterns that is Type A or Type B, as formulated by Friedman and Rosenman (1959) has received considerable attention because of attempts to reduce the nebulous social class stress areas to a more refined understanding of individual stressors. Type A behavior is defined as an overt behavior syndrome or style of living characterized by excesses of competitiveness, striving for achievement, aggressiveness, sometimes stringently oppressed, time urgency acceleration of common activities, restlessness, hostility, hyperalertness, explosiveness, speech amplitude, tenseness of facial musculature, and feelings of struggle against limitations

of time and the insensitivity of the environment. The converse of this type behavior called Type B is marked by the absence of Type A characteristics.

A prospective study by Jenkins, et al (1974) of 2,750 employed men who completed a computer scored test questionnaire measuring the coronary prone Type A behavior pattern, showed that high scorers had twice the incidence of new coronary diseases as low scorers over a four year period. Jenkins and his colleagues suggests that such a behavior pattern is prospectively linked to the pathogenesis of coronary heart disease and that their test questionnaire is a valid means of measuring some of the ways in which behavior contributes to the coronary risk.

Type A men who self-reference are also reported by Lovallo and Dickin (1980) to have higher resting blood pressure and greater cutaneous vasoconstriction, suggesting a higher tonic level of cardiovascular activity.

In a more recently reported study (Williams, et al, 1980), 71% of 319 patients who were Type A were found to have at least one significant coronary artery occlusion of 75% or greater. In contrast only 56% of the 105 non-Type A patients had a significant occlusion. These data equate to a crude relative odds of 2.3 and the authors consider this confirmation of earlier findings reported by a number of other investigators. The authors have also reported the association of Type A behavior and atherosclerosis is at least as strong in women as it is in men.

Thomsell (1979) thinks that psychosocial factors may contribute to the development of clinical coronary heart disease by (1) accelerating atherosclerosis via voluntary acts affecting conventional risk factors such as cigarette smoking, diet and physical activity as well as through neuro-hormonal pathways affecting blood pressure, lipid metabolism, and coagulating mechanisms and (2) by directly influencing the myocardium in

the cardiovascular system, thereby precipitating acute episodes of coronary heart disease.

Kaplan (1978) has presented evidence that psychogenic stress raises blood pressure by activation of the sympathetic nervous system by one or more neurogenic pathways. His evidence includes the findings that plasma catecholamines are elevated in some hypertensives and that levels of enzymes involved in the biosynthesis of norepinephrine were higher in tissue from hypertensive men. Louis, Doyle, et al (1973) had earlier reported a close correlation between systolic blood pressure and plasma noradrenaline levels.

3.5 Summary

The pathogenesis and epidemiology of cardiovascular diseases have been summarized in this report. The risk factors, biochemical pathways and mechanisms of the various disease components and manifestations have been enumerated and discussed. This process may well serve the purpose of identifying response variables for environmental studies as well as indicating elements which need to be controlled for (or considered) in future research study designs.

Risk factors have been deduced from epidemiological studies using cross-sectional prospective cohort, and case-control designs. Biochemical pathways have been identified generally from laboratory and clinical trials, while mechanisms, i.e., interaction of biochemical activity with social and environmental factors have been inferred from clinical and epidemiological studies.

This report has the potential to provide one of the bases for planning a research protocol to study the effects of noise on the cardiovascular

system. For example, if hypertension is to be the response variable for investigating the effects of noise, then the control variables and intervening variables can be identified for consideration. The control variables may include age, race, and sex and the intervening variables may be PRA, catecholamines, etc.

SELECTED REFERENCES

CARDIOVASCULAR DISEASES: PATHOLOGY AND PATHOGENESIS

Cassel, J.: Studies of Hypertension in Migrants, in Paul, O. (ed.), Epidemiology and Control of Hypertension, New York and London, Stratton Intercon Medical Book Corp., pp.41-61, 1975.

Cowley, A.W., Jr.: Perspectives on the Physiology of Hypertension. Cardiovascular Clinics 9(1): 1-22, 1978.

Guyton, A.C.: Textbook of Medical Physiology 4th Edition, Philadelphia, W.B. Saunders, 1971.

Haddy, F.J.: Mechanism Prevention and Therapy of Sodium-Dependent Hypertension. American Journal of Medicine 69: 746, 1980.

Hollander, W.: Role of Hypertension in Atherosclerosis and Cardiovascular Disease. American Journal of Cardiology 38: 786, 1976.

Johnson, J.G. and Muirhead, E.E.: Vascular Complications of the Hypertensive State, in Hunt, J.C., et al., (eds.), Hypertension Update, Bloomfield, NJ, Health Learning Systems, Inc., pp. 38-51, 1980.

Kottke, B.A. and Subbiah, M.T.: Pathogenesis of Atherosclerosis. Mayo Clinic Proceedings 53: 35-48, 1978.

Kuller, L., Lilienfeld, A. and Fisher, R.: An Epidemiological Study of Sudden and Unexpected Deaths in Adults. Medicine 46: 341, 1967.

Laragh, J.H.: Renin-Sodium Profiling is Helpful for Modern Management of Hypertensive Patients, in Rappaport, E. (ed.), Current Controversies in Cardiovascular Disease, Philadelphia, W.B. Saunders, pp. 521-548, 1980.

Lown, B.: Sudden Cardiac Death: The Major Challenge Confronting Cardiology. American Journal of Cardiology 43: 313, 1979.

Maseri, A., Chierchia, S. and L'Abbate, A.: Pathogenetic Mechanisms Underlying the Clinical Events Associated with Atherosclerotic Heart Disease. Circulation 62(suppl V): 3-10, 1980.

Oliva, Philip B.: Pathophysiology of Acute Myocardial Infarction. Annals of Internal Medicine 94: 236, 1981.

Popma, J.J. and Conti, C.R.: Acute and Chronic Ischemic Heart Disease: Coronary Artery Spasm, in Braun, E.W. (ed.), Current Cardiology, Vol. 2, Boston, Houghton Mifflin, pp. 230-239, 1980.

Ross, R. and Glomset, J.A.: The Pathogenesis of Atherosclerosis. New England Journal of Medicine 295: 369-377, 420-425, 1976.

Smith, J.B., Araki, H. and Lefer, A.M.: Thromboxane A_2, Prostacyclin and Aspirin: Effects on Vascular Tone and Platelet Aggregation. Circulation 62(suppl V): 19-25, 1980.

Stemerman, M.B.: Atherosclerosis: The Etiologic Role of Blood Elements and Cellular Changes. Cardiovascular Medicine 3: 17, 1978.

Strong, C.G.: The Renal Pressor and Depressor Systems: Actions and Interactions, in Hunt, J.C., et al., (eds.), Hypertension Update, Bloomfield, NJ, Health Learning Systems, Inc., pp. 125-131, 1980.

Warren, S.E. and O'Connor, D.T.: Does a Renal Vasodilator System Mediate Racial Differences in Essential Hypertension? American Journal of Medicine 69: 425, 1980.

Wissler, R.W.: Principles of the Pathogenesis of Atherosclerosis, in Braunwald (ed.), Heart Disease, Philadelphia, W.B. Saunders, pp. 1221-1245, 1980.

SELECTED REFERENCES

CARDIOVASCULAR DISEASES: EPIDEMIOLOGY

Abrahams, D.G., Alele, C.A. and Barnard, B.G.: The Systemic Blood Pressure in a Tural West African Community. West African Medical Journal 9:45-58, 1960.

Adams, J.M.: Some Racial Differences in Blood Pressure and Morbidity in a Group of White and Colored Workmen. American Journal of Medical Science 184:342, 1932.
Cited in Gillum, R.F.: Pathophysiology of Hypertension in Blacks and Whites, Hypertension 1(5):463-475, 1979.

Ahrens, E.H., et al.: The Influence of Dietary Fats on Serum-Lipid Levels in Man. Lancet 1:943, 1957.
Cited in McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Akinkugbe, O.O.: High Blood Pressure in the African, Edinburgh, Churchill Livingston, 1972.

Alexander, S.: Effects of Cold on the Cardiovascular System. The Practitioner 213:785-789, 1974.

Antonovsky, A.: Social Class and the Major Cardiovascular Diseases. Journal of Chronic Diseases 21:65-106, 1968.

Armstrong, M.L., Megan, M.B., Warner, E.D.: Intimal Thickening in Normocholesterolemic Rhesus Monkeys Fed Low Supplements of Dietary Cholesterol. Circulation Research 34:647, 1974.
Cited in Stamler, J.: Research Related to Risk Factors. Circulation 60(7): 1575-1587, 1979.

Armstrong, M.L.: Regression of Atherosclerosis, in Paoletti, R., Gotto, A.M., Jr. (eds.), Atherosclerosis Reviews 1, New York, Raven Press, p. 137, 1976.
Cited in Stamler, J.: Research Related to Risk Factors. Circulation 60(7):1575-1587, 1979.

Ayman, D. and Frank, J.E.: Nature of the Symptoms Associated with Essential Hypertension. Archives of Internal Medicine 67:679, 1941.

Barrett-Connor, E., Criqui, M.H., Klauber, M.R. and Holdbrook, M.: Diabetes and Hypertension in a Community of Older Adults. American Journal of Epidemiology 113(5):479-488, 1981.

Boyd, E.M., Bereziuk, W.D.: Facts and Fallacies Regarding the Blood Pressure of Different Regional and Racial Groups. Circulation 8:652, 1953.

Bunker, D.E., et al.: Blood-Lead and Cadmium in Human Hypertension. Journal of Environmental Pathology and Toxicology 4:1, 5:281-287, 1980.

Benson, H., Kotch, J.B. and Crossweller, K.D.: Stress and Hypertension: Interrelations and Management. Cardiovascular Clinics 9(1):113-124, 1978.

Bevan, A.T., Honour, A.J. and Stott, F.H.: Direct Arterial Pressure Recordings in Unrestricted Man. Clinical Science 36:329, 1969.

Borhani, N.O., Hechter, H.H. and Breslow, L.: Report of a Ten-Year Follow-up Study of the San Francisco Longshoremen, Mortality from Coronary Heart Disease and From All Causes. Journal of Chronic Diseases 16:1251, 1963.

Borhani, N.O., Hechter, H.H. and Breslow, L.: A Longitudinal Study of Blood Pressure. Angiology 15:545-555, 1964.

Boyle, E., Jr.: Biological Patterns in Hypertension by Race, Sex, Body Weight and Skin Color. Journal of the American Medical Association 213: 1637-1643, 1970.

Braunwald, E.: Coronary Spasm and Acute Myocardial Infarction - New Possibility for Treatment and Prevention. New England Journal of Medicine 299: 1301, 1978. Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

Byrne, D.G. and Whyte, H.M.: Life Events and Myocardial Infarction Revisited: The Role of Measures of Individual Impact. Psychosomatic Medicine 42(1):1-10, 1980.

Carroll, R.E.: The Relationship of Cadmium in the Air to Cardiovascular Disease Death Rates. Journal of the American Medical Association 198: 267-269, 1969.

Cassel, J.: Studies of Hypertension in Migrants in Epidemiology and Control of Hypertension, Paul, O. (ed.), New York and London, Stratton Intercon Medical Book Corp., pp. 41-61, 1975(a).

Cassel, J.: An Epidemiological Perspective of Psychosocial Factors in Disease Etiology. American Journal of Public Health 64(11):1040-1043, 1975(b).

Chapman, J.M.: Diseases of the Circulation in Preventive Medicine, Clark, D.W. and MacMahon, B. (eds.), Boston, Little, Brown and Co., 1967.

Cobb, L.A., Hallstrom, A.P., Weaver, D.W., Copass, M.K., Haynes, B.E.: Clinical Predictors and Characteristics of the Sudden Cardiac Death Syndrome, in Proceedings of the First US-USSR Symposium on Sudden Death, Yalta, October 3-5, 1977, Bethesda, MD, U.S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, DHEW publication no. (NIH) 79-1670, 1979.
Cited in Lown, Desmond: Sudden Cardiac Death, 1978. Circulation 60(7): 1593-1598, 1979.

Comstock, G.W.: An Epidemiologic Study of Blood Pressure Levels in a Biracial Community in the Southern United States. American Journal of Hygiene 65:271-314, 1957.

Comstock, G.W.: Water Hardness and Cardiovascular Disease. American Journal of Epidemiology 110:375-400, 1979.

Connor, W.E.: The Effects of Dietary Lipid and Sterols on the Sterol Balance, in Jones, R.J. (ed.), Atherosclerosis Proceedings of the Second International Symposium, New York, Springer-Verlag, pp. 253-261, 1970.
Cited by McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Cottingham, E.M., Matthews, K.A., Talbott, E. and Kuller, L.H.: Environmental Events Preceeding Sudden Death in Women. Psychosomatic Medicine 42(6): 567-574, 1980.

Crepet, M., Gobbato, F. and Scansetti, G.: Cardiovascular Changes in Lead Workers. Mineiva Medica 47:1910-1918, 1956.

Dahl, L.K.: Salt and Hypertension. American Journal of Clinical Nutrition 25:231-244, 1972.

Detre, K., Hultgren, H., Takaro, T.: VA Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. III. Methods and Baseline Characteristics Including Experience with Medical Treatment. American Journal of Cardiology 40:212-225, 1977.
Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Doll, R. and Peto, R.: Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors. British Medical Journal 2:1525-1536, 1976.

Doyle, A.E. and Lovell, R.R.H.: Blood Pressure and Body Build in Men in Tropical and Temperate Australia. Clinical Science 20:243, 1961.

Duke University of Medicine Center: Collaborative Group for Study of Stroke in Young Women: Oral Contraceptives and Stroke in Young Women. Journal of the American Medical Association 231:718-722, 1975.

El-Maraghi, N.R.H., Genley, H.J.: Recurrent Myocardial Infarction in a Young Man Due to Coronary Artery Spasm Demonstrated at Autopsy. Circulation 61:199, 1980.
Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

Epstein, F.H., Ostfeld, A.D.: The Epidemiology of High Blood Pressure. Geographic Distributions and Etiological Factors. In Stamler, J., Stamler, R., Pullman, T. (eds.), The Epidemiology of Hypertension. New York: Grune and Stratton, p. 133, 1967.

Evans, D.A., Gillett, M.C. and Hannaman, C.H.: Alcohol and Coronary Heart Disease. American Heart Journal 100:6:896-900, 1980.

Feinleib, M., Simon, A.B., Gillum, R.F. and Margolis, J.R.: Prodromal Symptoms and Signs of Sudden Death. Circulation 51/52:155-159, 1975. Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Fejfar, Z.: Some Aspects of the Epidemiology of Arterial Hypertension, in Stamler, J., Stamler, R. and Pullman, T.N. (eds.), The Epidemiology of Hypertension, New York, Grune and Stratton, Inc., 1967.

Fieser, L.E. and Fieser, M.: Steroids, New York, Reinhold Publishing, Corp., pp. 26, 53, 70, 1950.
Cited in McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Franklin, R.B., Smith, R.H. and Burham, W.A.: Cardiovascular Survey of 275 Adult Male Koreans, I. Blood Pressure. Military Medicine 138:214-218, 1973.

Freis, E.D.: Rebutal; Appraisal of Antihypertensive Drug Therapy. Circulation 50:9-10, 1974.

Friedman, M., Manwaring, J.H., Rosenman, R.H., Donlon, G., Ortega, P., and Grube, S.M.: Instantaneous and Sudden Death: Clinical and Pathological Differentiation in Coronary Artery Disease. Journal of the American Medical Association 225:1319-1328, 1973.

Friedman, M. and Rosenman, R.H.: Association of Specific Overt Behavior Pattern with Blood and Cardiovascular Findings: Blood Cholesterol Level, Blood Clotting Time, Incidence of Arcus Senilis and Clinical Coronary Artery Disease. Journal of the American Medical Association 169: 1286-1296, 1959.

Friedman, G.D., Loveland, D.B., Ehrlich, S.P.: Relationship of Stroke to Other Cardiovascular Disease. Circulation 38:553-541, 1968. Cited in Ostfeld, A.M.: A Review of Stroke Epidemiology. Epidemiologic Reviews 2:136-152, 1980.

Galyean, J.R., III: Risk Factors for Coronary Heart Disease. Southern Medical Journal 71(6):696-704, 1978.

Gillum, R.F.: Pathophysiology of Hypertension in Blacks and Whites. Hypertension 1(5):468-475, 1979.

Gordon, T. and Kannel, W.B.: Predisposition to Atherosclerosis in the Head, Heart, and Legs. Journal of the American Medical Association 221(7):661-666, 1972.

Green, L.W.: Manual for Scoring Socioeconomic Status for Research on Health Behavior. Public Health Reports - 1980, U. HEW 91(3):215-217, 1976.

Greene, W.A., Goldstein, S., and Moss, A.J.: Psychosocial Aspects of Sudden Death. Archives of Internal Medicine 129:725-731, 1972.
Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Hamilton, M., Pickering, G.V., Roberts, J.A.F., and Sowry, G.S.C.: The Aetiology of Essential Hypertension, I. The Arterial Pressure in the General Population. Clinical Science 13:11, 1954.

Harburg, E., Gleibermann, L., Roeper, P., Schork, M.A., Schull, W.J.: Skin Color, Ethnicity and Blood Pressure: Detroit, Part I. Blacks. American Journal of Public Health 68:1177, 1978.

Harburg, E., Erfurt, J.C., Havenstein, L.S., Chape, C., Shull, W.J., and Schork, M.A.: Socio-ecological stress, suppressed hostility, skin color, and black-white male blood pressure: Detroit. Psychosomatic Medicine 35(4):276-296, 1973.

Harlan, W.R., Sharrett, A.R., Weill, H., Turino, G.M., Borhani, N.O., and Resneko, L.: Impact of the Environment on Cardiovascular Disease, AHA Task Force Report. Circulation 63(1):243A-245A, 1981.

Harlan, W.R.: Physical and Psychosocial Stress and the Cardiovascular System. Circulation 63(1):266A-271A, 1981.

Havlik, R.J. and Feinleib, M. (eds.), Proceedings of the Conference on the Decline in Coronary Heart Disease Mortality, sponsored by the National Heart, Lung, and Blood Institute, NIH Publication No. 79, 1610, May 1979.

Haynes, S.G., Levine, S., Scotch, N., Feinlieb, M. and Kannel, W.B.: The Relationship of Psychosocial Factors to Coronary Heart Disease in the Framingham Study. I. Methods and Risk Factors. American Journal of Epidemiology 107(5):362-83, 1978.

Haynes, S.G. and Feinleib, M.: Women, Work and Coronary Heart Disease: Prospective Findings from the Framingham Study. American Journal of Public Health 70(2):133-41, 1980.

Keys, A., Anderson, J.T., Grande, F. Serum Cholesterol Response to Changes in the Diet: IV. Particular Saturated Fatty Acids in the Diet. Metabolism 14:776-787, 1965.

Keys, A., Menotti, A., Karvonen, M.J., Aravanis, C., Blackburn, H., Buzina, R., Djordjevic, B.S., Dontas, A.S., Fidanza, F., Keys, M.H., Kromhout, D., Nedeljkovic, S., Punsar, S., Seccareccia, F., Stanganelli, L. The Diet and 15-Year Death Rate in the Seven Countries Study. American Journal of Epidemiology 124(6):903-915, 1986.

Kinsell, L.W., Michaels, G.D., Partridge, J.W., Boling, L.A., Margen, S. Effect of Dietary Fat on Serum Cholesterol in Man. American Journal of Clinical Nutrition 17:281-295, 196.
Cited in Shekelle, R.B., et al.: Diet, Serum Cholesterol, and Death from Coronary Heart Disease. New England Journal of Medicine 304(2):65-75, 1981.

Kannel, W.B., Wilson, W. Stamler, R., Cole, D.S. and Hayvent, S.L.: Effects of Race, Blood Pressure in Coronary Deaths. Journal of the American Medical Association 242:1973, 1979.

Kuller, L.H. and Cassel, J.C. Psychosocial Factors in Essential Hypertension: Recent Epidemiologic and Animal Experimental Evidence. American Journal of Epidemiology 90:170-81, 1969.

Herbeden, W.: Commentaries on the History and Cure of Disease, London, 1802.

Heyman, A., Karp, H.R., Heyden, S., Bartel, A., Cassel, J.C. Tyroler, H.A., and Hames, C.G.: Cerebrovascular Disease in the Biracial Population of Evans County, Georgia. Archives of Internal Medicine 128:949-955, 1971.

Hillis, L.D., Braunwald, E.: Coronary Artery Spasm. New England Journal of Medicine 299:695, 1978.
Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

Hinkle, L.E., Jr., Whitney, L.H., et al.: Occupation, Education and Coronary Heart Disease. Science 161:233-245, 1968.

Hollander, W.: Hypertension, Antihypertensive Drugs and Atherosclerosis. Circulation 48:1112-1127, 1973.

Holme, I., Helgeland, A., Hjerman, I., Leren, P. and Lund-Larsen, P.G.: Four Year Mortality by Some Socioeconomic Indicators: The Oslo Study. Journal of Epidemiology and Community Health 34:48-52, 1980.

Holmes, T.H. and Rahe, R.H.: The Social Readjustment Rating Scale. Journal of Psychosomatic Research 11:213-218, 1967.

Hsu, Y.H., Yu, C.T., and Lou, D.A.: Arteriosclerosis in Experimental Lead Poisoning. Chung Hua I Hsueh Tsa Chih 43:886-894, 1957.

Huchard, H.: Maladies du coeur et des vaisseaux. Paris, Doin, 1889.

Hudson, H.E., Gilcreas, F.W.: Health and Economic Aspects of Water Hardness and Corrosiveness. Journal American Water Works Association 68:201-204, 1976.
Cited in Comstock, G.W.: Water Hardness and Cardiovascular Diseases. American Journal of Epidemiology 110:375-400, 1979.

Hypertension Detection and Follow-up Program Cooperative Group: Five-year Findings of the Hypertension Detection and Follow-up Program. I. Reduction in Mortality of Persons with High Blood Pressure, Including Mild Hypertension. Journal of the American Medical Association 242:2562-2571, 1979.
Cited in Oetfeld, A.M.: A Review of Stroke Epidemiology. Epidemiologic Reviews 2:136-152, 1980.

Jacobs, C.F. and Langdon, R.A.: Cardiovascular Deaths and Air Pollution in Charleston, S.C. Health Services Reports 87:623-732, 1972.

Janeway, T.C.: A Clinical Study of Hypertensive Cardiovascular Disease. Archives of Internal Medicine 12:735, 1913.
Cited in Pickering, G.: Hypertension. In Keogh, J.R. (ed.), Hypertension Manual, New York, Dun-Donnelley Pub. Corp., 1974.

Jenkins, C.D., Rosenman, R.H. and Zyzanski, S.J.: Prediction of Clinical Coronary Heart Disease by a Test for the Coronary-Prone Behavior Pattern. New England Journal of Medicine 290:1271-1275, 1974.

Jenkins, C.D., Tuthill, R.W., Tannenbaum, S.I., and Kirby, C.: Social Stressors and Excess Mortality from Hypertensive Diseases. Journal of Human Stress 5(3):29-40, 1979.

Jick, H., Dinan, B. and Rothman, K.J.: Oral Contraceptives and Non-Fatal Myocardial Infarction. Journal of the American Medical Association 239(14): 1403-1406, 1978.

Kannel, W.B. and Gordon, T., (eds.): The Framingham Study, An Epidemiologic Investigation of Cardiovascular Disease. Supt. of Documents, U.S. Government Printing Office, 1970.

Kannel, W.B.: Current Status of the Brain Infarction Associated with Occlusive Arterial Disease. Stroke 2:295-318, 1971.

Kannel, W.B., Wolf, P.A., and Dawber, T.R.: An Evaluation of the Epidemiology of Atherothrombotic Brain Infarction. Milbank Memorial Fund Quarterly 53: 405-448, 1975.
Cited in Kuller, L.H.: Epidemiology of Stroke, in Schoenberg, B.S. (ed.), Advances in Neurology, New York, Raven Press, 1978(b).

Kaplan, B.H., Cassel, J.C., Tyroler, H.A., Cornoni, J.C., Kleinbaum, D.G., and Hames, C.G.: Occupational Mobility and Coronary Heart Disease. Archives of Internal Medicine 128:938-942, 1971.

Kaplan, B.H., University of North Carolina at Chapel Hill: Personal Communication, 1975.

Kaplan, N.M.: Stress, the Sympathetic Nervous System and Hypertension. Journal of Human Stress 4(3):29-34, 1978.

Katz, L.N., Stamler, J., Pick, R.: Nutrition and Atherosclerosis, Philadelphia Lea and Febiger, 1958.
Cited in Stamler, J.: Research Related to Risk Factors. Circulation 60(7): 1575-1587, 1979.

Keen, B.N., Mammill, J.F.: Anthropathology of Arterial Tension. Archives of Internal Medicine 83:355, 1949.

Keil, J.E., Sandifer, S.H., Loadholt, C.B., Boyle, E., Jr.: Prevalence of Coronary Heart Disease in Charleston, South Carolina. Unpublished report, MUSC, Charleston, South Carolina, 1974.

Keil, J.E.: Hypertension: Effects of Social Class and Racial Admixtures in a Negro Community of Charleston, South Carolina. Doctoral Dissertation, University of North Carolina at Chapel Hill, 1975.

Keil, J.E.: Fourteen-Year Mortality in the Charleston Heart Study. Unpublished report, University of North Carolina at Chapel Hill, 1976.

Keil, J.E. and Cowan, B.: Prevalence of hypertension in females of Punjab State, India: Relationship with Age, Residence, Heart Rate, Occupation and Obesity. Human Biology 49(4):641-650, 1977(b).

Keil, J.E., Tyroler, H.A., Sandifer, S.H., and Boyle, E., Jr.: Hypertension: Effects of Social Class and Racial Admixture. American Journal of Public Health 67(7):634-639, 1977(b).

Keil, J.E., Loadholt, C.B., Sandifer, S.H. and Boyle, E., Jr.: Effects of Education and Skin Color on Blood Pressure. American Journal of Public Health 71: In Press, 1981(a).

Keil, J.E., Loadholt, B., Sandifer, S.H., and Boyle, E., Jr.: Predictors of AMI in Charleston, S.C. Unpublished data, University of South Carolina School of Public Health and Medical University of South Carolina. Unpublished Data, 1981(b).

Keys, A.: Diet and the Epidemiology of Coronary Heart Disease. Journal of the American Medical Association 164:1912, 1957.
Cited in McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Keys, A.: Dietary Survey Methods in Studies on Cardiovascular Epidemiology. Voeding 26:464-483, 1965.
Cited in Shekelle, R.B., et al.: Diet, Serum Cholesterol and Death from Coronary Heart Disease. New England Journal of Medicine 304(2):65-70, 1981.

Klein, B.E.K., Cornoni, J.C., Jones, F., and Boyle, E., Jr.: Overweight Indices as Correlates of Coronary Heart Disease and Blood Pressure. Human Biology 45(3):329-340, 1973.

Kleinbaum, D.G., Kupper, L.L., Cassel, J.C., and Tyroler, H.A.: Multivariate Analysis in Risk of Coronary Heart Disease in Evans County, Georgia. Archives of Internal Medicine 128:943-948, 1971.

Kobayashi, J.: On Geographical Relationship Between the Chemical Nature of River Water and Death-Rate from Apoplexy. Berichte des Ohara Institute fur landwirtschaftliche Biologie 11:12-21, 1957.

Krueger, D.E., Ellenberg, S.S., et al.: Fatal Myocardial Infarction and the Role of Oral Contraceptives. American Journal of Epidemiology 111(6): 655-674, 1980.

Krieger, H., Morton, N.E., Mi, M.P., Azevedo, A., Freire-Maia, A., Yasuda, N.: Racial Admixture in Northeastern Brazil. Ann Hum Genet 29:113, 1965.

Kuller, L.H.: Epidemiology of Cardiovascular Diseases: Current Perspectives. American Journal of Epidemiology 104:419-436, 1976.

Kuller, L.H.: Syndromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Kuller, L.H.: Epidemiology of Stroke. In Schoenberg, B.S. (ed.), Advances in Neurology. New York, Raven Press, 1978(b).

Kurtzke, J.F.: in Cerebrovascular Survey Report (Joint Council Subcommittee on Cerebrovascular Disease of National Institute of Neurological and Communicative Disorders and Stroke and National Heart and Lung Institute), Rochester, MN, Whiting Press, pp. 213-242, 1976.
Cited in Kuller, L.H.: Epidemiology of Stroke, in Schoenberg, B.S. (ed.), Advances in Neurology, New York, Raven Press, 1978(b).

Laragh, J.H.: An Approach to the Classification of Hypertensive States. Hospital Practice 9:61-73, January 1974.

Ledingham, J.M.: The Etiology of Hypertension. The Practioner, Symposium on Hypertension 207:5-19, 1971.

Lew, E.A.: High Blood Pressure, Other Risk Factors and Longevity: The Insurance Viewpoint, in Laragh, J.H. (ed.), Hypertension Manual. New York, Yorke Medical Books, Dun-Donnelly Pub. Corp., 1974.

Long, E.R.: The Development of our Knowledge of Arteriosclerosis, in Cowdry, E.V. (ed.), Arteriosclerosis: A Survey of the Problem, New York, MacMillan Company, pp. 19-52, 1933.
Cited in McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Louis, W.J., Doyle, A.E., Anavekar, S.N., and Chua, K.G.: Sympathetic Activity and Essential Hypertension. Clinical Science and Molecular Medicine 45:119s-121s, 1973.

Lovallo, W.R. and Pishkin, V.: Type A Behavior, Self Involvement, Autonomic Activity, and the Traits of Neuroticism and Extroversion. Psychosomatic Medicine 42(3):329-334, 1980.

Lown, B., Ruberman, W.: The Concept of Precoronary Care. Modern Concepts in Cardiovascular Disease 39:97, 1970.
Cited in Lown, Bernard: Sudden Cardiac Death - 1978. Circulation 60(7): 1593-1599, 1979.

Lown, B., Wolf, M.A.: Approaches to Sudden Death from Coronary Heart Disease. Circulation 44:130, 1971.
Cited in Lown, Bernard: Sudden Cardiac Death - 1978. Circulation 60(7): 1593-1599, 1979.

Lown, B., Calvert, A.F., Armington, R., Ryan, M.: Monitoring for Serious Arrhythmias and High Risk of Sudden Death. Circulation 52(Supplement III): III-189, 1975.
Cited in Lown, Bernard: Sudden Cardiac Death - 1978. Circulation 60(7): 1593-1599, 1979.

Lown, B., Verrier, R.L., Rabinowitz, S.H.: Neural and Psychologic Mechanisms and the Problem of Sudden Cardiac Death. American Journal of Cardiology 39:890, 1977.
Cited in Lown, Bernard: Sudden Cardiac Death - 1978. Circulation 60(7): 1593-1599, 1979.

Lown, Bernard: Sudden Cardiac Death - 1978. Circulation 60(7):1593-1599, 1979.

Mahley, R.W., Bersot, T.P., Innerarity, T.L., Lipson, A., and Margolis, S.: Alterations in Human High-Density Lipoproteins, With or Without Increased Plasma-Cholesterol, Induced by Diets High in Cholesterol. Lancet 2:807, 1978.
Cited in McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Mahomed, F.A.: Chronic Bright's Disease without Albuminuria. Guys Hospital Report 25:295-416, 1881.

Mann, G.V., Shaffer, R.D., Anderson, R.S., and Sandstead, H.H.: Cardiovascular Disease in the Masai. Journal of Atherosclerotic Research 4:289, 1964.
Cited in McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Maseri, A., Severi, S., DeNes, M., et al.: Variant Angina: One Aspect of a Continuous Spectrum of Vasospastic Myocardial Ischemia. American Journal of Cardiology 42:1019, 1978.
Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

Massey, E.W., Shoenberg, D.G., Schoenberg, B.S.: Mortality in 33 Countries from Diseases of the Nervous System. (Submitted for publication).
Cited in Schoenberg, B.S.: Epidemiology of Cerebrovascular Disease. Southern Medical Journal 72(3):331-336, 1979.

Masters, A.M., Dublin, L.I., and Marks, H.H.: The Normal Blood Pressure Range and Its Unusual Complications. Journal of the American Medical Association 143:1464-1470, 1950.

Matsumoto, N., Whisnant, J.P., Kurland, L.T., Okazaki, H.: Natural History of Stroke in Rochester, Minnesota 1955 through 1969: An Extension of a Previous Study, 1945 through 1954. Stroke 4:21-29, 1973.

Mattson, F.H., Erickson, B.A., and Kligman, A.M.: Effects of Dietary Cholesterol on Serum Cholesterol in Man. The American Journal of Clinical Nutrition 25:589, 1972.

McCaughan, D.: Comparison of an Electronic Blood Pressure Apparatus with A Mercury Manometer. Journal of Advancement of Medical Instrumentation, November/December 1966.

McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Medalie, J.H. and Goldbourt, Uri: Angina Pectoris Among 10,000 Men. American Journal of Medicine 60:910-920, 1976.

Menotti, A. and Puddu, V.: Ten Year Mortality from Coronary Heart Disease among 172,000 Men Classified by Occupational Physical Activity. Scand Journal of Work Environment and Health 5:100-108, 1979.

Metropolitan Life Insurance Company: Statistical Bulletin 56:2-5, 1975.

Miall, W.E.: Heredity and Hypertension. The Practitioner 207:20-27, 1971.

Morse, W.R., McGill, M.D., and Beh, Y.T.: Blood Pressure Amongst Aboriginal Ethnic Groups of Szechwan, Province, West China. Lancet 1:966-967, 1937.

Mudge, G.H., Jr., Goldberg, S., Gungher, S., Mann, T., Grossman, W.: Comparison of Metabolic and Vasoconstrictor Stimuli on Coronary Vascular Resistance in Man. Circulation 59:544, 1979.
Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

Murrill, R.I.: A Blood Pressure Study of the Natives of Ponape Island, East Carolines. Human Biology 21:47-59, 1949.

Myasnikov, A.L., Chazov, E.I., Koshevnikova, T.L., Nikolaeva, L.F.: Some New Data on the Occurrence of Coronary Thrombosis in Conjunction with Atherosclerosis. Journal of Atherosclerosis Research 1:401, 1961.
Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

National Health Survey: Hypertension and Hypertensive Heart Disease in Adults, U.S. 1960-1962. USDHEW, Vital and Health Statistic Series II, No. 13, Washington, D.C., U.S. Government Printing Office, 1966.

Noakes, T.D. and Opie, L.H.: Marathon Running and the Heart: The South African Experience. American Heart Journal 98(5):669-671, 1979.

Oberman, A., Jones, W., and Riley, C.: Natural History of Coronary Artery Disease. Bulletin of New York Academy of Medicine 48:1109-1125, 1972.
Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Oglesby, Paul (ed.), Epidemiology and the Control of Hypertension, New York, Stratton Intercontinental Book Corporation, 1975.

Oliva, P.B., Breckinridge, J.C.: Arteriographic Evidence of Coronary Arterial Spasm in Acute Myocardial Infarction. Circulation 56:366, 1977.
Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

Oparil, S. and Haber, E.: The Renin-Angiotensin System. New England Journal of Medicine 291:389-401, 1974.

Ostfeld, Adrian M.: A Review of Stroke Epidemiology. Epidemiologic Reviews 2:136-152, 1980.

Paffenbarger, R.S., Notkin, J., Krueger, D.E., Wolf, P.A., Thorne, M.C., LeBauer, E.J., Williams, J.L.: Chronic Disease in Former College Students. II. Methods of Study and Observations on Mortality from Coronary Heart Disease. American Journal of Public Health 56:962, 1966.
Cited in Stamler, J.: Research Related to Risk Factors. Circulation 60(7): 1575-1587, 1979.

Page, L.B. and Sidd, J.J.: Medical Management of Primary Hypertension, I. New England Journal of Medicine 287:1074-1081, 1973.

Patel, Y.C., Eggen, D.A., and Strong, J.P.: Obesity, Smoking and Atherosclerosis. Atherosclerosis 36:481-490, 1980.

Perper, J.A., Kuller, L.H., and Cooper, M.: Arteriosclerosis of Coronary Arteries in Sudden, Unexpected Death. Circulation 51:27-33, 1975.
Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Petitti, D.B., Wingerd, J.D., Pellegrin, F., and Ramcharan, S.: Risk of Vascular Disease in Women; Smoking, Oral Contraceptives, Noncontraceptive Estrogens and Other Factors. Journal of the American Medical Journal 242(11):1150-1154, 1979.

Pick, R., Johnson, P.J., Glick, G.: Deleterious Effects of Hypertension on the Development of Aortic and Coronary Atherosclerosis in Stumptail Macaques (Macaca Speciosa) on an Atherogenic Diet. Circulation Research 35:472, 1974.
Cited in Stamler, J.: Research Related to Risk Factors. Circulation 60(7):1575-1587, 1979.

Pickering, G.: High Blood Pressure, Second Edition. New York, Grune and Stratton, Inc., 1968.

Pickering, G.: Hypertension, Definitions, Natural Histories and Consequences, in Laragh, J.H. (ed.), Hypertension Manual, New York, Yorke Medical Books, Dun-Donnelly Pub. Corp., 1974.

Platt, R.: The Nature of Essential Hypertension. Lancet 2:55-57, 1959.

Rahe, R.H., McKean, J.D., Arthur, R.J.: A Longitudinal Study of Life Change and Illness Patterns. Journal of Psychosomatic Research 10:355-366, 1967.

Rahe, R.H. and Lind, E.: Psychosocial Factors and Sudden Cardiac Death. Journal of Psychosomatic Research 15:19-24, 1971.
Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Reichenbach, D.D., Moss, N.S., and Meyer, E.: Pathology of the Heart in Sudden Cardiac Death. American Journal of Cardiology 39:865-872, 1977.
Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Reid, D.D., Hamilton, P.J.S., et al.: Smoking and Other Risk Factors for Coronary Heart-Disease in British Civil Servants. The Lancet 2:979-984, November 6, 1976.

Robinson, W.S.: Ecological Correlations and the Behavior of Individuals. American Sociological Review 15:351, 1950.
Cited in McGill, Henry C., Jr.: The Relationship of Dietary Cholesterol to Serum Cholesterol Concentration and to Atherosclerosis in Man. The American Journal of Clinical Nutrition 32:2664-2702, 1979.

Rose, G.A., Holland, W.W., and Crowley, E.A.: A Sphygmomanometer for Epidemiologists. Lancet 1:296-300, 1964.

Rose, G.A. and Blackburn, H.: Cardiovascular Survey Methods. Geneva, WHO Monograph Series No. 56, 1968.

Ryan, M., Lown, B., Horn, H.: Comparison of Ventricular Ectopic Activity During 24-Hour Monitoring and Exercise Testing in Patients with Coronary Heart Disease. New England Journal of Medicine 292:224, 1975.
Cited in Lown, Bernard: Sudden Cardiac Death - 1978. Circulation 60(7): 1593-1599, 1979.

Schanberg, S.M., Stone, R.A., Kirshner, N., Gunnells, J.C., and Robinson, R.R.: Plasma Dopamine B-Hydroxylase: A Possible Aid in the Study and Evaluation of Hypertension. Science 183:523-526, 1974.

Schoenberg, Bruce S.: Epidemiology of Cerebrovascular Disease. Southern Medical Journal 72(3):331-336, 1979.

Schroeder, H.A.: Relation Between Hardness of Water and Death Rates from Certain Chronic and Degenerative Diseases in the United States. Journal of Chronic Diseases 12:586-591, 1960.

Schroeder, H.A.: Municipal Drinking Water and Cardiovascular Death Rates. Journal of the American Medical Association 195(2):125-129, 1966.

Schroeder, H.A., et al.: Essential Metals in Man: Magnesium. Journal of Chronic Diseases 21:815-841, 1969(a).

Schroeder, H.A.: The Water Factor. New England Journal of Medicine 280: 836-838, 1969(b).

Scotch, N., Gampel, G., Abramson, J.H., and Slome, C.: Blood Pressure Measurements of Urban Zulu Adults. American Heart Journal 61:173-177, 1961.

Seltzer, C.C.: Smoking and Coronary Heart Disease: What Do We Believe? American Heart Journal 100(3):275-280, 1980.

Shaper, A.G.: Soft Water, Heart Attacks, and Stroke. Journal of the American Medical Association 230:130-131, 1974.
Cited in Comstock, G.W.: Water Hardness and Cardiovascular Diseases. American Journal of Epidemiology 110:375-400, 1979.

Sharrett, A.R., Feinleib, M.: Water Constituents and Trace Elements in Relation to Cardiovascular Diseases. Preventive Medicine 4:20-36, 1975.

Sharrett, A.R.: The Role of Chemical Constituents of Drinking Water in Cardiovascular Diseases. American Journal of Epidemiology 110(4):401-419, 1979.

Shekelle, R.B., Shryock, A.M., Paul, O., Lepper, M., Stamler, J., Liu, S., and Raynor, W.J., Jr.: Diet, Serum Cholesterol and Death from Coronary Heart Disease. New England Journal of Medicine 304(2):65-70, 1981.

Shurtleff, D.: Some Characteristics Related to the Incidence of Cardiovascular Disease and Death: Framingham Study, 16-year Follow-up, in Kannel, W.B., Gordon, T. (eds.), The Framingham Study, An Epidemiological Investigation of Cardiovascular Disease. Sect. 26, Washington, D.C., U.S. GPO, 1970. Cited in Kuller, L.H.: Epidemiology of Cardiovascular Diseases: Current Perspectives. American Journal of Epidemiology 104:425-456, 1976.

Stamler, J.: Lectures in Preventive Cardiology. New York, Grune and Stratton, Inc., 1967.

Stamler, J.: Research Related to Risk Factors. Circulation 60(7):1575-1587, 1979.

Stamler, R., Stamler, J., Riedlinger, W.F., Algera, G., and Roberts, R.H.: Weight and Blood Pressure. Journal of the American Medical Association 240(15):1607-1610, 1978.

Stewart, I.M.G.: Headache and Hypertension. Lancet 1:1261, 1953.

Suls, J., Gastorf, J.W., and Witenberg, S.H.: Life Events, Psychological Distress and the Type A Coronary-Prone Behavior Pattern. Journal of Psychosomatic Research 23:315-319, 1979.

Syme, S.L., Oakes, T.W., Friedman, G.D., Fieldman, R., Siegelaub, A.B., and Collen, M.: Social Class and Racial Differences in Blood Pressure. American Journal of Public Health 64(6):619-620, 1974.

Syme, S.L.: Social and Psychological Risk Factors in Coronary Heart Disease. Modern Concepts of Cardiovascular Disease XLIV(4):17-21, 1975.

Takahashi, E.: Discussion of Socioeconomic Factors in the Epidemiology of Hypertensive Disease, in Stamler, J., Stamler, R., and Pullman, T.N. (eds.), The Epidemiology of Hypertension. New York, Grune and Stratton, Inc., 1967.

Theorell, T., Lind, E., and Floderus, B.: The Relationship of Disturbing Life Changes and Emotions to the Early Development of Myocardial Infarction and Other Serious Illnesses. International Journal of Epidemiology 4: 281-293, 1975.
Cited in Kuller, L.H.: Prodromata of Sudden Death and Myocardial Infarction. Advances in Cardiology 25:61-72, 1978(a).

Theorell, T.: Life Events and Disease: Psychosocial Precipitation of Episodes of Clinical Coronary Heart Disease. Journal of Psychosomatic Research 23:403-404, 1979.

Toole, J.: Diagnosis and Management of Stroke; Dallas, American Heart Association, 1979, in Stroke Rehabilitation, Fergenson, J.S. in Current Concepts of Cerebrovascular Disease 15(6):21-26, 1980.

Tyroler, H.A., Heyden, S., Bartel, A., Cassel, J.C., Cornoni, J., Hames, C.G., and Kleinbaum, D.: Blood Pressure and Cholesterol as Coronary Heart Disease Risk Factors. Archives of Internal Medicine 128:907-914, 1971.

Tyroler, H.A., Heyden, S., and Hames, C.G.: Weight and Hypertension; Evans County Studies of Blacks and Whites. Presented at the Epidemiology of Hypertension - 2nd International Symposium, Chicago, September 18, 1974.

Tyroler, H.A., James, S.A.: Blood Pressure and Skin Color. American Journal of Public Health 68:1170, 1978.

U.S. DHEW: Smoking and Health, A Report of the Surgeon General, DHEW Publication N: (DHS) 79-50066, 1979.

Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of Treatment on Morbidity in Hypertension. Results in Patients with Diastolic Pressures Averaging 115 through 129 mm Hg. Journal of the American Medical Association 202:1028-1034, 1967.
Cited in Ostfeld, A.M.: A Review of Stroke Epidemiology. Epidemiologic Reviews 2:136-152, 1980.

Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of Treatment on Morbidity in Hypertension. II. Results in Patients with Diastolic Pressures Averaging 90 through 114 mm Hg. Journal of the American Medical Association 213:1143-1152, 1970.
Cited in Ostfeld, A.M.: A Review of Stroke Epidemiology. Epidemiologic Reviews 2:136-152, 1980.

Volhard, F. and Fahr, T.: Die Brightsche Nierenkrankheit. Berlin, Springer, 1914.

Von Basch, S.S.K. Uber Latente Arteriosclerose und Deren Beziehung zu anderen Begleiter Scheinungen. Vienna, Urban und Schwartzenberg, 1893.

Wagner, E.H.: Hypertension - Seminar to Community Medicine Department. University of North Carolina, 1974.

Weisfeldt, M.L., Flaherty, J.T.: Myocardial Infarction, in Willerson, J.T., Sanders, C.A. (eds.), Clinical Cardiology. New York, Grune and Stratton, p. 346, 1977.
Cited in Willerson, J.T. and Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.

Williams, R.B., Haney, T.L., et al. Type A Behavior, Mortality and Coronary Atherosclerosis. Psychosomatic Medicine 42(6):539-549, 1980.

Willerson, J.T., Buja, L.M.: Cause and Course of Acute Myocardial Infarction. American Journal of Medicine 69:903-914, 1980.